EXHIBIT 1

To M. Kim Declaration

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

HALOZYME, INC. Plaintiff v. MICHELLE K. LEE, performing the functions and duties of Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, Defendant.	Civil Action No. 16-CV-01580 CMH (JFA)

CORRECTED OPENING EXPERT REPORT OF SAMUEL ZALIPSKY, Ph.D., REGARDING NON-OBVIOUSNESS OF THE PENDING CLAIMS OF THE '171 APPLICATION

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I. INTRODUCTION

1. My name is Samuel Zalipsky, Ph.D. I have been asked to submit this report on behalf of Halozyme, Inc. ("Halozyme") in the above-captioned action. I have been retained as an expert by Halozyme to study and provide my opinions on the invention claimed in, and the validity of the pending claims in U.S. Patent Application Serial No. 11/238,171 (the "'171 Application") (A1-A324).

2. I understand that Halozyme has filed this action against Defendant, Michelle K. Lee, in her official capacity as Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office ("Defendant" or "USPTO") before the Eastern District of Virginia pursuant to 35 U.S.C. § 145.

3. I understand that Halozyme is seeking a judgment that it is entitled to a patent for the invention specified in Claims 264-266, 278, 291-293, 295-298, 300, and 303 of the '171 Application ("Pending Claims") (A1248-A1250) (attached as Exhibit 1), contrary to the final decision by the Patent Trial and Appeal Board ("PTAB" or "Board") in an appeal under 35 U.S.C. § 134(a), affirming the Examiner's obviousness rejection of the Pending Claims under 35 U.S.C. § 103(a)[1] based on three prior art references: (1) WO 2004/078140 titled "Soluble Hyaluronidase Glycoprotein (sHASEGP), Process for Preparing the Same, Uses and Pharmaceutical Compositions Comprising Thereof" to Bookbinder *et al.* ("'140 Bookbinder") (A1332-A1546); (2) U.S. Patent No. 5,766,897 titled "Cysteine-PEGylated Proteins" to Braxton ("Braxton") (A1547-A1581); and (3) U.S. Patent No. 6,552,170 titled "PEGylation Reagents and

[1] The changes to 35 U.S.C. § 103 in the AIA do not apply to any applications filed before March 16, 2013. *See* MPEP Section 2159.01. Thus, the '171 Application, which was filed on September 27, 2005, is governed by pre-AIA 35 U.S.C. 103(a).

Compounds Formed Therewith" to Thompson *et al.* ("Thompson") (A1596-A1620). I understand that Halozyme also contests the Board's affirmance of the Examiner's non-statutory obviousness-type double patenting rejections of the Pending Claims over U.S. Patent Nos. 7,767,429 titled "Soluble Hyaluronidase Glycoprotein (sHASEGP), Process for Preparing the Same, Uses and Pharmaceutical Compositions Comprising Thereof" to Bookbinder *et al.* (claims 9 and 10) (A1629-A1720), 7,846,431 titled "Soluble Glycosaminoglycanases and Methods of Preparing and Using Soluble Glycosaminoglycanases" to Bookbinder *et al.* (claims 4 and 5) (A1831-A1946) and 7,829,081 titled "Soluble Glycosaminoglycanases and Methods of Preparing and Using Soluble Glycosaminoglycanases" to Bookbinder *et al.* (claims 5 and 6) (A2057-A2170) in view of Braxton and Thompson.

4. I have been asked to provide my opinions on the following matters and expect to testify as such if called as a witness including the areas of: (1) the field of art pertinent to the '171 Application; (2) the level of ordinary skill in the art as of the priority date of the '171 Application; (3) the manner in which a person of ordinary skill in the art of the '171 Application would understand the contents of various patents, products, publications and other materials that were publicly available prior to the priority date of the '171 Application; (4) general PEGylation (the attachment of polyethylene glycol (PEG) moieties to a biologically relevant molecule, for example, a protein) techniques known as of the priority date of the '171 Application; (5) the invention described and claimed in the '171 Application; (6) whether '140 Bookbinder is a proper prior art reference; (7) whether '140 Bookbinder, Braxton and Thompson in combination with each other and/or the general knowledge of a person of ordinary skill in the art disclose each and every element of one or more of the Pending Claims; (8) whether one of skill in the art would be motivated to combine '140 Bookbinder, Braxton and Thompson and whether one of

skill would have a reasonable expectation of success; (9) the non-statutory obviousness-type double patenting rejections of the Pending Claims over U.S. Patent Nos. 7,767,429 (claims 9 and 10), 7,846,431 (claims 4 and 5) and 7,829,081 (claims 5 and 6) in view of Braxton and Thompson; and (10) secondary considerations of non-obviousness.

5. In this report, I give my opinions as to the meaning that would have been given to these terms and phrases by a person of ordinary skill in the art as of the priority date of the '171 Application.

6. This report sets forth my opinions based on the information identified and the analysis I have performed through the date of this report. This report, and my opinions contained herein, is subject to change or modification if additional relevant information becomes available that bears on my analysis. I understand that further discovery will be conducted in this case, and new evidence may be uncovered. I also understand that Defendant may submit expert testimony, and that new testimony or materials may be introduced at the trial in this action. I also understand that I may be asked at the trial to express opinions regarding matters that are raised at the trial. Accordingly, I reserve the right to supplement or amend my opinions to this report if additional information that affects my opinions becomes available.

7. If asked to do so at the trial, I am prepared to explain in detail, with appropriate visual aids, the invention described and claimed in the '171 Application, and the content and applicability of the prior art. Such testimony may include, for example, background materials relevant to the '171 Application and the prior art; the conclusions I have reached in this report; and/or the basis for those opinions.

8. As set forth in this report, including all attachments, I have concluded that the Pending Claims are not obvious, and that the objective, or secondary evidence that courts have

used to assess non-obviousness further support a finding of non-obviousness of the Pending Claims of the '171 Application.

A. Qualifications

9. A copy of my curriculum vitae, which contains information pertaining to my education, experience, professional activities, publications, presentations, lectures and patents is attached as Exhibit 2 and summarized below.

10. I currently serve as an independent consultant focusing in the area of the design, development and use of carrier mediated drug delivery systems. I have been active in the pharmaceutical and biotechnology industries for over 24 years. Over these years, I have variously supported, designed, and managed the development of formulation, bioconjugation, and delivery of macromolecules, proteins, peptides, lipids, saccharides, and oligonucleotides. I pioneered various PEG functionalization and conjugation methods, contributing to the commercialization of the well-known, trailblazer bioconjugate- and nanoparticulate-based products, PEG-Intron and DOXIL.

11. More specifically, I was Vice President of Research at PhaseRx Pharmaceuticals in Seattle, Washington from 2010-2011 where I focused on the development of polymer-based technology for delivery of oligonucleotides. I also served as Vice President of Technology Development at Intradigm in Palo Alto, California where I oversaw all aspects of drug delivery technology from 2007 to 2010. From 1999 to 2007, I was a Senior Research Fellow and Director of Protein & Linker Chemistry at ALZA Corporation in Mountain View, CA where I introduced and developed new macromolecular conjugates for protein delivery. I was also a Senior Research Investigator at SEQUUS Pharmaceuticals, Inc. in Menlo Park, CA where I designed, synthesized and formulated biocompatible polymers (e.g., PEG), as conjugates with

bioactive compounds from 1992 to 1999. From 1987 to 1991, I was Director of Chemical Research at Enzon, Inc. in South Plainfield, NJ where I developed new methods for preparing reactive polymers and their therapeutic protein conjugates. From 1986-1987, I was a Senior Chemist at Genesis Laboratories in Minneapolis, MN where I developed new methods for protein-protein conjugation.

12. In addition to my extensive experience in the pharmaceutical and biotechnology industries, I have also served as a Visiting Associate Professor in the Chemistry Department at Rutgers University in Piscataway, NJ from 1990-1992. During this time, my research focused on novel functionalized biocompatible polymers, drug carriers and hydrogels. I also supervised post-doctoral fellows and graduate students.

13. I have authored 90 publications, including authoritative reviews, in the field of biocompatible polymeric carriers of drugs and biologics and conjugates of biomacromolecules with lipids, peptides and drugs, including PEGylation. For example, my 1995 review articles in Bioconjugate Chemistry (Functionalized poly(ethylene glycol) for preparation of biologically relevant conjugates, 6:150) and Advanced Drug Delivery Reviews (Chemistry of polyethylene glycol conjugates with biologically active molecules, 16:157) summarize the state of this field since its inception. They are widely cited, even in many current publications. I also edited a state of the art book, "Poly(ethylene glycol) chemistry and Biological Applications," 1997, American Chemical Society Books, Washington DC.

14. I have given numerous lectures and presentations world-wide on these topics, particularly in the fields of functionalized polymers, including PEGs for drug delivery. I am also an inventor of over 50 United States patents, most of which are dealing with PEGylation of biological macromolecules and nanoparticles.

15. I periodically serve as a manuscripts reviewer for a number of technical journals in the field, including Bioconjugate Chemistry, Analytical Biochemistry, Biomacromolecules, and Biopolymers: Peptide Science. I have served on the Editorial Advisory Boards of the following journals: Bioconjugate Chemistry, and International Journal of Peptide Research and Therapeutics, and Journal of Bioactive & Compatible Polymers.

16. I have a Ph.D. in Chemistry (Bio-Organic division) from the University of Minnesota, a M.S. degree (with distinction) in Chemistry from The Hebrew University of Jerusalem, Israel and a B.S. degree in Chemistry and Biochemistry from the same university. I have taught courses in the field of chemistry, biology and applications of bioconjugates.

17. I have not provided expert testimony either by deposition or at trial within the last four years.

B. Materials Considered

18. As part of my preparation for writing this report, and in reaching the opinions and conclusions described herein, I have considered the ’171 Application, the respective file history, the appeal briefings, PTAB Decision of Appeal and Request for Rehearing concerning Appeal No. 2014-001770; the Complaint and Answer filed in this Action; scientific or technical references cited herein, certain documents produced by the parties in this litigation, all other documents cited or listed in this report, and materials listed in Exhibit 3, all of which I incorporate by reference in my report. I have also considered various other sources of information, such as patents and publications that were available to persons of ordinary skill in the art as of the priority date of the ’171 Application, including any citations identified in this report. My opinions are further based upon my over 30 years of education, training, research,

collaborations, and related publications, knowledge and personal and professional experience in the relevant art.

19. My analysis of the materials produced in this case is ongoing. If new materials are made available to me, I will continue to review such materials. Therefore, this report represents only those opinions I have formed to date, and I reserve the right to revise, supplement, and amend the opinions stated herein based on new information and on my continuing analysis of the materials already produced. For example, I reserve the right to supplement the opinions in this report based on the future deposition of Defendant's expert(s) to be identified in this case, future positions to be taken by Defendant or its expert(s), additional documents, reports, testimony, or other information provided by Defendant or any witnesses, any orders from the Court, or as otherwise necessary.

C. Compensation

20. I am being compensated for my work on this case at my standard consulting rate of $600 per hour. I am also being reimbursed for expenses that I incur. My compensation is not contingent upon the outcome of this litigation, or upon the results of my study or the substance of my testimony. I have no other interests in this litigation or with any of the parties.

II. SUMMARY OF OPINIONS

21. This section contains a summary of the primary opinions and conclusions that I provide in this report.

22. It is my opinion that all of the Pending Claims of the '171 Application are not obvious, and that objective, secondary evidence of non-obviousness further support a finding of non-obviousness of the Pending Claims at-issue. In particular, on July 27, 2016, the PTAB issued a Decision on Appeal affirming the Examiner's Final Rejection of all Pending Claims

(A2210-A2222) (attached as Exhibit 4) under 35 U.S.C. § 103(a) based on three prior art references: (1) '140 Bookbinder (A1332-A1546) (attached as Exhibit 5); (2) Braxton (A1547-A1581) (attached as Exhibit 6); and (3) Thompson (A1596-A1620) (attached as Exhibit 7). On October 20, 2016, the PTAB issued a Decision on Request for Rehearing maintaining the affirmance of the Final Rejection (A2236-A2239). As an initial matter, I note that the '171 Application claims priority to 11/065,716, filed on February 23, 2005 (the "'716 Application") (HALOZ0000001-HALOZ0000325) that issued as U.S. Patent 7,871,607 on January 18, 2011 (the "'607 Patent"). I have examined the disclosure of the '716 Application and it shows that the inventors were in possession of the subject matter claimed in the '171 Application Pending Claims, and further enabled such claims. I have been advised by counsel that if so, '140 Bookbinder is not prior art, and thus it is my opinion that the Pending Claims are not obvious. Alternatively, I disagree that the Pending Claims are obvious based on these three prior art references for several reasons as explained in further detail in my report:

(a) '140 Bookbinder, Braxton and Thompson in combination do not disclose each and every limitation of the Pending Claims of the '171 Application;

(b) a person of ordinary skill in the art would not have been motivated to make and/or would not have had a reasonable expectation of success in achieving a PEGylated human-derived hyaluronidase pharmaceutical composition with three to six PEG moieties for systemic administration and activity at neutral pH because multi-PEGylation of human-derived hyaluronidase with three to six PEG moieties via lysine residues was unknown until the filing of the '171 Application, and the number of lysine residues available for conjugation provided no guidance to target conjugation with three to six PEG moieties;

(c) a person of ordinary skill in the art would not have been motivated to make and/or would not have had a reasonable expectation of success in achieving a PEGylated human-derived hyaluronidase pharmaceutical composition with three to six PEG moieties for systemic administration and activity at neutral pH because of a lack of understanding of human-derived hyaluronidase's mechanism of action and attendant uncertainties about whether such a PEGylated human-derived hyaluronidase with three to six PEG moieties would be suitable as a pharmaceutical composition formulated for systemic administration;

(d) a person of ordinary skill in the art would not have been motivated to make and/or would not have had a reasonable expectation of success in achieving a PEGylated human-derived hyaluronidase pharmaceutical composition with three to six PEG moieties for systemic administration and activity at neutral pH because, as discussed in my report, the state of the art with similar enzymes that act on macromolecular substrates and are rapidly cleared from bloodstream via the mannose receptor, would strongly suggest that a multi-PEGylation approach is not likely to succeed;

(e) a person of ordinary skill in the art would not have been motivated to make and/or would not have had a reasonable expectation of success in achieving a PEGylated human-derived hyaluronidase pharmaceutical composition with three to six PEG moieties for systemic administration and activity at neutral pH because several alternative approaches with a much higher probability of success were available to modify a protein such a hyaluronidase, for example, super-sialylation and glycan remodeling; and

(f) a person of ordinary skill in the art would not have been motivated to make and/or would not have had a reasonable expectation of success in achieving a PEGylated

hyaluronidase pharmaceutical composition with three to six PEG moieties for systemic administration and activity at neutral pH following the teachings of Braxton and/or Thompson because both references teach site-specific PEG conjugation to cysteine residues of various proteins whereas the human-derived hyaluronidase disclosed in the '171 Application utilizes amine-directed PEG conjugation to lysine residues, and further, do not teach PEGylating hyaluronidase, much less with three to six PEG moieties.; and

(g) secondary factors of non-obviousness further establish that the invention claimed in the '171 Application is not obvious.

23. The Board's also affirmed the Examiner's non-statutory obviousness-type double patenting rejections of the Pending Claims over U.S. Patent Nos. 7,767,429 (claims 9 and 10), 7,846,431 (claims 4 and 5) and 7,829,081 (claims 5 and 6) in view of Braxton and Thompson. I disagree that the Pending Claims are obvious variants over U.S. Patent Nos. 7,767,429 (claims 9 and 10), 7,846,431 (claims 4 and 5) and 7,829,081 (claims 5 and 6) in view of Braxton and Thompson for several reasons as explained in further detail in my report:

(a) the Pending Claims are different from U.S. Patent Nos. 7,767,429 (claims 9 and 10), 7,846,431 (claims 4 and 5) and 7,829,081 (claims 5 and 6); and

(b) the Pending Claims are patentable distinct from U.S. Patent Nos. 7,767,429 (claims 9 and 10), 7,846,431 (claims 4 and 5) and 7,829,081 (claims 5 and 6) in view of Braxton and Thompson.

24. I have reviewed the Opening Expert Report of Bruno Flamion, M.D., Ph.D., Regarding Non-Obviousness of the Pending Claims of the '171 Application ("Flamion Opening Report"), and the information and conclusions in his report further inform my opinions here.

III. LEGAL STANDARDS

25. In this section, I describe my understanding of certain legal principles. I have been informed of these legal principles by Halozyme's attorneys. I am not an attorney, and I am relying only on instructions from Halozyme's attorneys for these legal principles.

A. Level of Ordinary Skill in the Art

26. I understand that central to the process of understanding the disclosures in a patent or patent application, and assessing the validity of a patent or patent application is the notion of a person of ordinary skill in the art ("POSITA").

27. I understand that a POSITA is a hypothetical person at the time of the invention who is presumed to be familiar with the relevant scientific field and its literature and used to analyze the prior art without the benefit of hindsight. A POSITA is presumed to be one who thinks along the lines of conventional wisdom in the art and is not one who undertakes to innovate, whether by extraordinary insights or by patient and often expensive systematic research.

28. I understand that the level of ordinary skill in the art may be determined by reference to certain factors, including (1) the type of problems encountered in the art; (2) prior art solutions to those problems; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the educational level of active workers in the field.

B. Priority Date

29. I understand that in order for claims in a pending patent application to obtain the benefit of an earlier filed application, the disclosure of the earlier filed application must be examined to assess whether that disclosure conveys to the POSITA ("Person Of Ordinary Skill In The Art") that the inventors were in possession of the subject matter claimed and that the

disclosure combined with knowledge in the art enabled one of skill to make the subject matter without undue experimentation. I understand these are referred to as the written description and enablement requirements. I understand this analysis may result in a publication being disqualified as prior art because that publication was not published a year before the priority date document and/or is not work by another.

C. Obviousness

30. I understand that under 35 U.S.C. § 103(a), "[a] patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in § 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains."

31. I understand that whether a claim would have been obvious is a legal conclusion based on underlying factual determinations. The factual determinations I must consider when evaluating whether the asserted claims would have been obvious to one of ordinary skill in the art include (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) the objective (secondary) evidence of non-obviousness.

32. I understand that a patent claim composed of several limitations is not proved obvious merely by demonstrating that each of its limitations was independently known in the prior art. In particular, I understand that identifying a reason or motivation why one of ordinary skill in the art at the relevant time would combine known elements can be important because inventions in most, if not all, instances rely upon building blocks since uncovered, and claimed

discoveries almost of necessity will be combinations of what, in some sense, is already known. Thus, to establish obviousness, there must be a finding that a person of ordinary skill in the art would have been motivated to combine the prior art in the way claimed by the Pending Claims of the '171 Application and had a reasonable expectation of success in doing so. Obviousness concerns with whether a skilled artisan not only could have made but would have been motivated to make the combinations or modifications of prior art to arrive at the claimed invention.

33. I also understand that, when making an obviousness determination, one must guard against the use of hindsight. In other words, one must be cautious to avoid reading into the prior art the teachings of the claimed invention at issued.

34. I understand that a prior art's speculative and tentative disclosure of what might or may explain the cause of a desired effect does not sufficiently direct or instruct one of skill in the art.

35. I understand that where a disclosed range is so broad as to encompass a very large number of possible distinct compositions, or where there are numerous parameters to try, or where the prior art merely teaches to pursue a general approach that seemed to be a promising field of experimentation, or gave only general guidance as to the particular form of the claimed invention or how to achieve it, it does not invite routine experimentation to discover optimum values.

36. I understand that certain factors, or secondary considerations, can support a finding of non-obviousness. I understand that those secondary considerations include: long-felt but unmet need, the failure of others, skepticism by experts, praise by others, teaching away by others, unexpected results of the invention, recognition of a problem, copying of the invention by competitors, and the invention's commercial success. I also understand that there must be a link

(or nexus) between the claimed invention and the secondary considerations before the evidence is relevant to the question of non-obviousness.

D. Nonstatutory Obviousness-Type Double Patenting

37. I understand that the obviousness double patenting analysis entails two steps: (1) construction of the claims in the earlier patent and the claim in the later patent to identify any differences; and (2) determination of whether the differences in subject matter between the claims render the claims patentably distinct.

38. I understand that for step 1, that it is important to bear in mind that comparison can be made only with what invention is claimed in the earlier patent, paying careful attention to the rules of claim interpretation to determine what invention a claim defines and not looking to the claim for anything that happens to be mentioned in it as though it were a prior art reference.

39. I understand that the key inquiry is the differences between the inventions defined by the conflicting claims and that the specification is only to be used to construe the meaning or scope of the claims.

40. I understand that a double patenting of the obviousness type rejection is analogous to a failure to meet the non-obviousness requirement of 35 U.S.C. § 103, except that the patent principally underlying the double patenting rejection is not considered prior art.

IV. THE LEVEL OF ORDINARY SKILL IN THE ART

41. In determining the characteristics of a hypothetical person of ordinary skill in the art of the ’171 Application at the time of the claimed invention, I considered several factors discussed above including the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the education level of active workers in the field. Finally, I placed myself back

at the time of the claimed invention, and considered the scientists, researchers and students who I had taught and with whom I had worked.

42. It is my opinion that a person of ordinary skill in the art in the field of the invention disclosed and claimed in the '171 Application would have earned a Ph.D. in biochemistry, molecular biology, physiology, pharmacology, or a related field, and at least four years of post-doctoral or industry experience studying protein and/or enzyme modification and conjugation.

V. TECHNOLOGY BACKGROUND

A. Use of Polymers in Drug Delivery

43. Drug delivery and drug formulation primarily focus on increasing the *in vivo* longevity, and rendering more favorable biodistribution and stability of drugs without significantly compromising the biological activity of the active ingredient. The use of proteins as therapeutic products presents unique challenges that limit its delivery as a drug, including short circulating half-life[2], low solubility, rapid kidney clearance and immunogenicity. Several potential approaches have emerged over the years to attempt to address these problems, including (1) manipulation of amino acid sequence to decrease immunogenicity and proteolytic cleavage, (2) fusion or conjugation to immunoglobulins and serum proteins such as albumin, (3) incorporation into drug delivery vehicles for protection and slow release, such as liposomes, and (4) conjugating to natural or synthetic polymers. Harris & Chess, *Effect of Pegylation on Pharmaceuticals*, NATURE REVIEW DRUG DISCOVERY 2(3):214-221 (2003), at 214 (HALOZ0000759-HALOZ0000766) ("Harris & Chess 2003").

[2] Circulating half-life time is commonly understood to be the time it takes for the administered drug concentration in blood to drop to one-half.

44. Conjugating proteins to polymers can act to stabilize the proteins in biological surroundings, such as the blood, and can provide *in vivo* protection against degradation, reduce antigenicity and immunogenicity, reduce toxicity and/or undesirable side effects, increase solubility and increase body residence time. Alteration of these properties by conjugation is achieved by shielding various sites of macromolecular drugs and proteins, or by simply dramatically increasing the size of the drug molecules. The amount of the conjugated polymer, both its molecular mass and the number of attachments, strongly influence properties of the conjugates.

45. Polymers are macromolecules made up of repeating units. Water-soluble polymers are of particular importance for protein conjugation because such polymers are very efficient at changing a protein's physical and biological properties. Some examples of water-soluble biocompatible polymers include dextran, polyethylene glycol ("PEG"), polyvinyl pyrrolidone ("PVP"), polyvinyl alcohol ("PAA"). *See, e.g.*, Wileman *et al.*, *Potential use of an asparaginase-dextran conjugate in acute lymphoblastic leukemia*, J. PHARM. PHARMACOL. 35:762-765 (1983) (HALOZ0000349-HALOZ0000352) ("Wileman 1983"); Sherwood *et al.*, *Enhanced plasma persistence of therapeutic enzymes by coupling to soluble dextran*, BIOCHEM. J. 164(2):461-464 (1977) (HALOZ0000326-HALOZ0000329) ("Sherwood 1977"); Katre, *The conjugation of proteins with polyethylene glycol and other polymers*, ADV. DRUG DEL. REV. 10:91-114 (1993) (HALOZ0000493-HALOZ0000516) ("Katre 1993"); Delgado *et al.*, *The uses and properties of PEG-linked proteins*, CRIT. REV. THERAPEUT. DRUG CARRIER SYS. 9(3,4):249-304 (1992) (HALOZ0000401-HALOZ0000458) ("Delgado 1992"); and Duncan and Spreafico, *Polymer Conjugates Pharmacokinetic Considerations for Design and Development*, CLIN. PHARMACOKINET. 27(4):290-306 (1994) (HALOZ0000517-HALOZ0000533) ("Duncan 1994").

Among these polymers, PEG is the most popular modifier of drugs, particularly proteins, and PEG conjugates are often used as a standard to which alternative polymer conjugates are compared. Kamada *et al.*, *Antitumor activity of Tumor Necrosis Factor-α conjugated with polyvinylpirrolidone on solid tumors in mice*, CANCER RES. 60:6416-6420 (2000) (HALOZ0000632-HALOZ0000637) ("Kamada 2000").

B. Polyethylene Glycol ("PEG") as a Polymer

46. PEG is a polymer widely used for conjugation with biologically relevant substances because it possesses a potentially favorable array of properties, including very low toxicity, excellent solubility in aqueous solutions, and extremely low immunogenicity and antigenicity as discussed above. Katre 1993; Zalipsky, *Chemistry of polyethylene glycol conjugates with biologically active molecules*, ADV. DRUG DELIV. REV. 16(2-3):157-182 (1995), at 158 (HALOZ0000534-HALOZ0000559) ("Zalipsky 1995").

47. PEG is synthesized by polymerization of ethylene oxide to form polymers with linear or branched shapes of different molecular masses. Figure 1 below shows examples of the structural formula of PEG molecules:

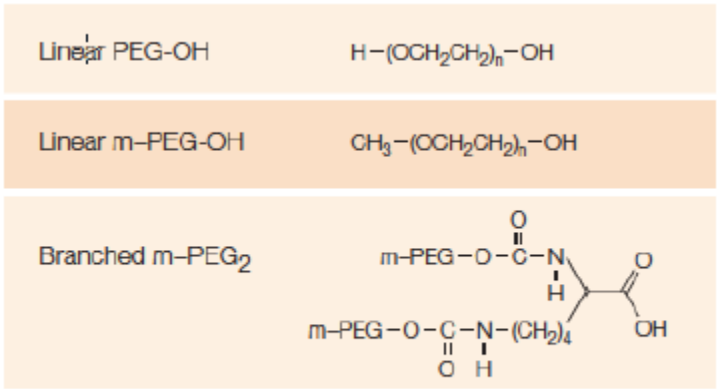

Figure 1 | **Structural formulae of polyethylene glycol (PEG) molecules.** m–PEG, monomethoxy–PEG.

Figure 1. Harris & Chess 2003, Fig. 1 at 215.

48. These PEG structures are then chemically functionalized on their end groups and attached to the drug of choice in a process called PEGylation. Most of the known examples of PEGylated drugs are PEG-protein conjugates. As of 2005, there existed many approaches to preparation of PEG-protein conjugates. *See, e.g.*, Zalipsky 1995; Veronese, *Peptide and protein PEGylation: a review of problems and solutions*, BIOMATERIALS 22:405-417 (2001) (HALOZ0000654-HALOZ0000666) ("Veronese 2001"); Roberts *et al.*, *Chemistry of peptide and protein PEGylation*, ADV. DRUG DEL. REV. 54:459-476 (2002) (HALOZ0000715-HALOZ0000732) ("Roberts 2002"). Even as of 2016, there is continued interest in development of many new approaches to preparation of PEG-protein conjugates, underscoring that PEGylation is an advancing art, i.e., publications today continue to address issues and obstacles that are being overcome for any specific protein. *See, e.g.*, Turecek *et al.*, *PEGylation of biopharmaceuticals: a review of chemistry and nonclinical safety information of approved drugs*, J. PHARM. SCI. 105:460-475 (2016) (HALOZ0000875-HALOZ0000890) ("Turecek 2016").

49. PEG conjugation can mask the protein's surface and increase the molecular size, thereby reducing its renal clearance and recognition by the immune system or degradation by proteolytic enzymes. Veronese 2001, at 406. Figure 2 below illustrates several potential advantages of a PEGylated protein, including the increase in size to reduce kidney filtration, increase in solubility due to PEG hydrophilicity, and decreased accessibility for proteolytic enzymes and antibodies:

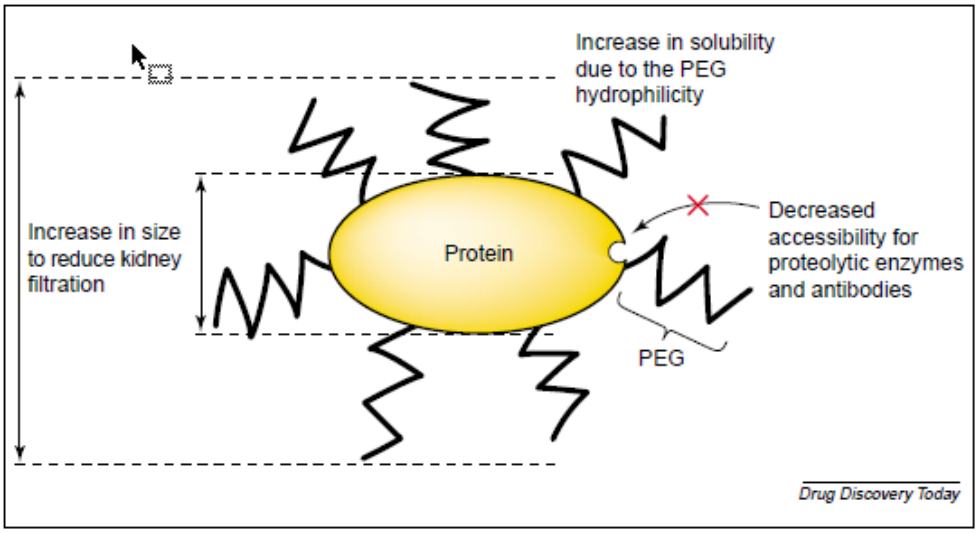

FIGURE 1

Main advantages of PEGylated protein. The figure represents a polymer-protein conjugate. The polymer, PEG, is shielding the protein surface from degrading agents by steric hindrance. Moreover, the increased size of the conjugate is at the basis of the decreased kidney clearance of the PEGylated protein.

Figure 2. Veronese and Pasut, *PEGylation, successful approach to drug delivery*, DRUG DISCOVERY TODAY 10(21):1451-1458 (2005), at Fig. 1 (HALOZ0000779-HALOZ0000786) ("Veronese 2005").

50. Researchers have noted as of the time of the invention and even more recently that while PEG conjugation can offer attractive properties (e.g., can shield antigenic epitopes of the polypeptide, thus reducing reticuloendothelial (RES) clearance and recognition by the immune system; increases the apparent size of the polypeptide, thus reducing renal filtration and altering biodistribution), many factors affect these properties, including (1) the number of PEG chains attached to the polypeptide, (2) the molecular weight and structure of PEG chains attached to the polypeptide, (3) the location of the PEG attachment sites on the polypeptide, and (4) the chemistry used to attach the PEG to the polypeptide. Roberts *et al.*, *Chemistry for peptide and protein PEGylation*, ADV. DRUG DELIV. REV. 64:116-127 (2012), at117 (HALOZ0000848-HALOZ0000859) ("Roberts 2012"); Katre 1993; Zalipsky 1995; Veronese 2001.

51. In fact, leading researchers in the field have noted: "Usually it is difficult to forecast with accuracy the pharmacokinetic behavior of native proteins even when their

structural properties are well known. The prediction becomes practically impossible in the case of PEG conjugates, where many new variables are added, such as the effect of molecular weight and shape of the polymer, extent of modification and site of PEG attachment. All these parameters affect, to different extents, the several biological processes, which are involved in the in vivo fate of the conjugate: glomerular filtration, stability, immunogenicity, tissue localization, cell uptake, liver excretion, etc. So far only few general rules may be drawn and unfortunately the PEG conjugates behavior must be verified by case by case experimentation only, as is evident from the many examples reported in this review." Caliceti and Veronese, *Pharmacokinetic and biodistribution properties of poly(ethylene glycol)-protein conjugates*, ADVANCED DRUG DELIVERY REVIEWS 55:1261–1277 (2003), at p.1274 (HALOZ0000742-HALOZ0000758) ("Caliceti 2003").

C. Success of PEGylation is Highly Protein Specific

52. There are many chemical approaches to PEGylation of proteins that a skilled artisan has to consider, including the chemistry of PEG attachment (either random or site-specific), what protein functional groups to modify, whether to use branched or linear PEGs, the molecular weight or size of the PEG, the number of PEG attachments (single versus multiple), stability/lability of the formed linkage(s), and even the nature of the end group on the conjugated PEG chains (*e.g.*, Thompson; Sherman *et al.*, *Role of the Methoxy Group in Immune Responses to mPEG-Protein Conjugates*, BIOCONJUGATE CHEM. 23:485-499 (2012) (HALOZ0000860-HALOZ0000874) ("Sherman 2012")). For example, PEG molecular weight has a great influence on the biological properties of conjugates. Veronese 2001, at 406. Yet this influence can move in different directions for balancing the desirable properties, such as preservation of activity and prolongation of *in vivo* circulation.

53. Perhaps even more importantly, the success of using PEGylation is still highly protein specific and depends on the protein's specific properties and mechanism of action. For example, PEGylating gulonolactone oxidase by two different methods did not improve any of its *in vivo* properties; specifically, the conjugates still retained their immunogenicity and did not show any lengthening in plasma lifetime in mice. Zalipsky 1995, at 164; Hadley and Sato, *Catalytic activity of administered gulonolactone oxidase polyethylene glycol conjugates*, ENZYME 42:255-234 (1989) (HALOZ0000369-HALOZ0000379) ("Hadley 1989"). Setbacks in development of PEGylated proteins were observed in all stages, sometimes even in late stage clinical trials. For example, Amgen's PEG-rhMGDF (recombinant human megakaryocyte growth and development factor) exhibited promising megacariocytes and platelets-stimulating activity in rodents, non-human primates, and initial human studies. However its development was stopped due to surprisingly strong immunogenic response in the treated patients, contrary to expectations. Neumann & Foote, *Megakaryocyte growth and development factor (MGDF): an Mpl ligand and cytokine that regulates thrombopoiesis*, CYTOKINES CELL MOL. THER. 6:47-56 (2000) (HALOZ0000703-HALOZ0000714) ("Neumann 2000"). This is despite the use of the human protein sequence and well-publicized propensity of PEGylated proteins to possess reduced immunogenicity compared to the parent proteins. *See, e.g.*, Fishburn, *The Pharmacology of PEGylation: Balancing PD with PK to Generate Novel Therapeutics*, J. PHARM. SCI. 97(10):4167-4183 (2008) (HALOZ0000797-HALOZ0000813) ("Fishburn 2008"); Katre 1993; Turecek 2016.

54. Historically, PEGylation was used for smaller proteins and enzymes acting on small substrates to increase their size to slow renal clearance and to reduce immunogenicity. Fishburn 2008 at Table 4. However, neither of these motivations is relevant with the human-

derived hyaluronidase (rHuPH20) claimed in the '171 Application because hyaluronidase is a large enzyme (approximately 60kDa) that acts on a very large substrate, hyaluronan, and its clearance is now understood to be mediated by mannose receptor uptake rather than a function of its size.

55. In the case of enzymes possessing high molecular weight substrates, like hyaluronidase, the application of PEG conjugation technology is very challenging, particularly where, as in the '171 Application, the claims are to a specific number of PEG molecules for a protein that is to be administered systemically and must act as a therapeutic on a large substrate. Veronese 2001, at 411. This is because increasing the extent of PEGylation interferes with the binding of macromolecular substrates. In contrast to enzymes acting on low molecular weight substrates, extensive PEGylation of enzymes acting on large molecular weight substrates typically results in a measurable loss of substrate binding and turnover activity, often leading to complete loss of potency. *See, e.g.*, Zalipsky 1995.

56. I authored a review paper in 1995 that discussed the impact of PEGylation on the selectivity of enzymes that act on large substrates including trypsin, chymotrypsin, and RNAse. Zalipsky 1995 at 164-166. Several other publications in the relevant time period also illustrate how enzymes with large substrates, such as proteases, show changes in reactant selectivity after PEGylation, namely that the ability to act on large substrates is dramatically diminished or even completely lost, depending on the extent of PEGylation, *i.e.*, number and size of the attached PEGs.

57. For example, PEGylated chymotrypsin loses large protein proteolytic activity, but still retains full activity on low molecular weight peptide substrates. Chiu *et al.*, *Enzymatic activity of chymotrypsin and its poly(ethylene glycol) conjugates toward low and high molecular*

weight substrates, BIOCONJUGATE CHEM. 4:290-295 (1993) (HALOZ0000487-HALOZ0000492) ("Chiu 1993"). As other example, PEGylated trypsin also changed the selectivity of the enzyme by losing proteolytic activity but retaining and even increasing activity to low molecular weight substrates. Zalipsky *et al.*, *Evaluation of new reagent for covalent attachment of polyethylene glycol to proteins*, BIOTECHNOL. APPL. BIOCHEM. 15:100-114 (1992) (HALOZ0000466-HALOZ0000481) ("Zalipsky 1992"); *see also* Zalipsky 1995 at 164-166. The increased activity could be due to the impact of PEG on the solubility/affinity of small substrates around the active site.

58. Another interesting example is lysozyme, a small protein possessing lytic activity toward a very large substrate, the bacterial cell wall peptidoglycan. When PEGylated, lysozyme shifts its optimal pH to a more acidic range, which is where chemical degradation of polysaccharides is more favorable. Nodake and Yamasaki, *Some Properties of a Macromolecular Conjugate of Lysozyme Prepared by Modification with a Monomethoxypolyethylene Glycol Derivative*, BIOSCI. BIOTECHNOL. BIOCHEM. 64(4):767-774 (2000) (HALOZ0000638-HALOZ0000645) ("Nodake 2000"). In this study, PEG-Lysozyme completely retained its ability to hydrolyze oligomeric β-1,4-N-acetylglucosamine, but markedly lost its activity in the *Micrococcus Luteus* assay. Similar observations were made in my laboratory in 2007, namely that even low levels of lysozyme PEGylation completely abolished the bacterial cell wall lysing ability. Zalipsky *et al.*, *Thiolytically Cleavable Dithiobenzyl Urethane-Linked Polymer–Protein Conjugates as Macromolecular Prodrugs: Reversible PEGylation of Proteins*, BIOCONJUGATE CHEM. 18:1869-1878 (2007) (HALOZ0000787-HALOZ0000796) ("Zalipsky 2007").

59. Other examples where PEGylation caused enzyme activity alteration in a substrate size-dependent manner include: Sphingomyelinase, alginate lyase, and RNAse. Matsuyama *et al.*, *Changes is enzymatic and membrane-adsorbing activities of Sphingomyelinase from Bacillus cereus by modification with polyethylene glycol derivative*, CHEM. PHARM. BULL. 40(9):2478-2482 (1992) (HALOZ0000482-HALOZ0000486) ("Matsuyama 1992"); Sakakibara *et al.*, *Preparation and properties of alginate lyase modified with Poly (ethylene Glycol)*, J. PHARM. SCI. 91(4):1191-1199 (2002) (HALOZ0000733-HALOZ0000741) ("Sakakibara 2002"); and Caliceti *et al.*, *Effects of monomethoxypoly(ethylene glycol) modification of ribonuclease antibody recognition, substrate accessibility and conformational stability*, J. MOLEC. RECOGN. 3(2):89-93 (1990) (HALOZ0000392-HALOZ0000396) ("Caliceti 1990"). All of these examples illustrate that when the extent of PEGylation (size and number of PEG chains linked per enzyme) is increased, activity towards macromolecular substrates may be changed, often with the result that activity is dramatically compromised, or even completely lost.

60. Yet another layer of uncertainty for PEG-proteins and extensions of their *in vivo* residence time arises when those proteins, such as the claimed PEGylated human-derived hyaluronidase (rHuPH20) with 3-6 PEG moieties, have exposed glycans with terminal galactose or mannose residues, which are now known to facilitate facile receptor-mediated clearance from circulation, which can be gradually slowed, but not eliminated. Studies have shown that there is variability in clearance in response to the degree of PEGylation for these types of proteins. *See, e.g.*, Berger, Jr. and Pizzo, *Preparation of polyethylene glycol-tissue plasminogen activator adducts that retain functional activity: Characteristics and behavior in three animal species*, BLOOD 71(6):1641-1647 (1988) (HALOZ0000353-HALOZ0000360) ("Berger 1988")

(PEGylated t-PA studies). Although it has been shown that both receptor- and nonreceptor-mediated clearance can be influenced by PEGylation, retaining biological activity and yet sufficiently masking the receptor interactions is a balancing act. Beauchamp *et al.*, *A New Procedure for the synthesis of polyethylene glycol-protein adducts; effects on function, receptor recognition, and clearance of superoxide dismutase, lactoferrin, and α_2-macroglobulin*, ANAL. BIOCHEM. 131:25-33 (1983) (HALOZ0000340-HALOZ0000348) ("Beauchamp 1983"). For example studies on PEGylated-asialofetuin showed that increasing the degree of PEGylation gradually decreased the uptake of the conjugates by the asialoglycoprotein receptor (Gal receptor of hepatocytes), but did not completely eliminate it. Roseng *et al.*, *Uptake, intracellular transport, and degradation of Polyethylene glycol-modified asialofetuin in hepatocytes*, J. BIOL. CHEM. 267(32):22987-22993 (1992) (HALOZ0000459-HALOZ0000465) ("Roseng 1992").

61. Finally, the art in 2005 was, unpredictable as to whether one could PEGylate with 3 to 6 moieties a human protein like hyaluronidase and still retain the desired activity for therapeutic performance for a pharmaceutical composition to be administered systemically. Human-derived hyaluronidase, the enzyme acting on a macromolecular substrate, hyaluronan (with molecular weight in the millions of Daltons), has exposed mannose residues, which are now known to be subject to a facile clearance via mannose receptors, which are present on dendritic cells and macrophages, as well as on Kupfer cells and on endothelial liver cells. These concerns become even less predictable when random, lysine-directed PEGylation is employed as was done to the claimed pharmaceutical composition of the '171 Application (comprising a PEGylated rHuPH20 with 3 to 6 moieties that is soluble at neutral pH and active), because the location of the PEG moieties on the protein cannot be controlled and could interfere with the active site on the protein. This is particularly true where one of skill would know that human-

derived hyaluronidase had 31 lysine residues that would be potential targets and likely would not be uniformly PEGylated in the same manner, molecule to molecule.

62. I note that site-specific PEGylation, which was developing in 1990's would have been a more favored approach for the human-derived hyaluronidase, rather than random PEGylation. *See, e.g.*, Goodson and Katre, *Site-directed PEGylation of recombinant interleukin-2 at its glycosylation site*, BIOTECHNOLOGY 8:343-346 (1990) (HALOZ0000397-HALOZ0000400) ("Goodson 1990"); and Braxton. This is because a skilled artisan is able to choose where in the protein sequence to position the PEG attachment(s), in a way that could potentially preserve activity and hinder or shield undesirable interaction, such as recognition and clearance via the exposed mannose residues. But there are limitations to this approach, as discussed *infra* in the context of, *e.g.*, cysteine conjugation.

63. Given these concerns and known issues related to human-derived hyaluronidase, a POSITA would have been motivated and had a more reasonable expectation of success using alternative approaches other than PEGylation to achieve prolonged circulation *in vivo*. Re-engineering of the exposed mannose-rich glycans of the protein would have been such a logical approach. One example of such an approach is the well-known case of the ARANESP product, where natural glycosylation of erythropoietin was changed by introduction of additional, new, fully sialylated glycans, which caused a marked prolongation in *in vivo* performance compared to the parent protein. Egrie and Browne, *Development and characterization of novel erythropoiesis stimulating protein (NESP)*, BRIT. J. CANCER 84(Suppl.):3-10 (2001) (HALOZ0000646-HALOZ0000653) ("Egrie 2001").

64. Another well-known approach is additional enzymatic glycosylation. *See, e.g.*, Gamblin *et al.*, *Glycoprotein Synthesis: An Update*, CHEM. REV. 109(1):131-163 (2009)

(HALOZ0000814-HALOZ0000847) ("Gamblin 2009"). This would allow enzymatic addition of sugars to the exposed mannose residues of the human-derived hyaluronidase, typically galactose, followed by terminal sialic acid residues. This would make these glycans look much like typical oligosaccharides of long-circulating glycoproteins, *e.g.*, immunoglobulins, and would likely achieve the objective of prolonged *in vivo* circulation. *See, e.g.*, Dwek, *Glycobiology: Toward understanding the function of sugars*, CHEM. REV. 96:683-720 (1996) (HALOZ0000560-HALOZ0000597) ("Dwek 1996"). In this way, sialylation typically masks the other sugar moieties, such as galactose and mannose, and prevents rapid uptake of the glycoproteins by the RES. I note that all the approaches discussed above were known and available for practice, and could have been applied to the human-derived hyaluronidase.

65. In my opinion, among the studied PEGylated proteins that have similar attributes to human-derived hyaluronidase, Tissue Plasminogen Activator (t-PA) can be viewed as a useful comparator for the uncertainties inherent in one of skill approaching the problem of how to make a pharmaceutical composition for systemic administration comprising a human-derived hyaluronidase with 3-6 PEG moieties. This is because both enzymes are glycosylated and contain exposed mannose glycans, and hence, are subject to fast mannose receptor-mediated clearance. Noorman *et al.*, *Inhibition of mannose receptor-mediated clearance of tissue-type plasminogen activator (t-PA) by dextran: a new explanation for its antithrombotic effect*, THROMB. HAESMOT. 78:1249-1254 (1997), at 1249 (HALOZ0000610-HALOZ0000616) ("Noorman 1997"); Lansink *et al.*, *Increased clearance explains lower plasma levels of tissue-type plasminogen activator by estradiol: Evidence for potently enhanced mannose-receptor expression in mice*, BLOOD 94(4):1330-1336 (1999) (HALOZ0000624-HALOZ0000631) ("Lansink 1999"); Hotchkiss *et al.*, *The influence of carbohydrate structure on the clearance of*

recombinant tissue-type plasminogen activator, THROMB. HAESMOT. 60(2):255-261 (1988), at 259 (HALOZ0000361-HALOZ0000368) ("Hotchkiss 1988").

66. Both have macromolecular substrates, and are approximately the same molecular size as albumin. Spellman *et al.*, *Carbohydrate structures of human tissue plasminogen activator expressed in Chinese hamster ovary cells*, *J. Biol. Chem.* 264(24):14100-14111 (1989) (HALOZ0000380-HALOZ0000391) ("Spellman 1989"). Comparison to albumin is only relevant in the sense that it is a non-glycosylated protein that stays in the circulation for days, and as a result, can be used as a carrier for drugs. Kratz *et al.*, *Probing the cysteine-34 position of endogenous serum albumin with thiol-binding doxorubicin derivatives. Improved Efficacy of an acid sensitive doxorubicin derivative with specific albumin-binding properties compared to that of the parent compound*, J. MED. CHEM. 45:5523-5533 (2002) (HALOZ0000667-HALOZ0000677) ("Kratz 2002").

67. Researchers encountered much difficulty in attempting to modify t-PA in a manner that would retain sufficient therapeutic activity and prolong half-life. In my opinion, these complexities and uncertainties highlight the inherent uncertainty that one of skill would have in approaching the problem, would select other methodologies, such as super-sialylation, and would not have a reasonable expectation for success for a three to six PEG, human-derived hyaluronidase. Berger 1988.

68. In my opinion, these studies highlight the complexities and uncertainties with working with enzymes that act on macromolecular substrates and are subject to mannose-receptor-mediated clearance, as is the case with human-derived hyaluronidase, and that the art pointed to other approaches than PEGylation. Moreover, as seen with rt-PA, while half-life was increased only slightly via PEGylation, retaining functional activity for therapeutic use proved to

be a difficult endeavor. In comparison, the results shown in the file history of '171 Application (Bookbinder declaration) for rHuPH20 with 3-6 PEG moieties, each of molecular weight 30 kDa, appear to be comparable, if not even more complex, than to the case of t-PA. These studies show the difficulty involved in balancing preservation of enzymatic activity and prolonging *in vivo* circulation by random amine-directed PEGylation of 3 to 6 PEG moieties for a pharmaceutical composition comprising human-derived hyaluronidase that is systemically administered and that is soluble and active at neutral pH, as the Pending Claims delimit.

VI. THE '171 APPLICATION

A. Priority Date

69. The '171 Application claims priority to U.S. Application No. 11/065,716, filed February 23, 2005 (the "'716 Application") (HALOZ0000001-HALOZ0000325), which issued as U.S. Patent No. 7,871,607 (the "'607 Patent").

70. Below is a chart that shows exemplary disclosures in the '716 Application that provide written description and enablement support for each of the Pending Claims of the '171 Application:

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
Claim 264. A pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein: the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule; the	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
hyaluronidase polypeptide is a human-derived hyaluronidase; and the composition is formulated for systemic administration.	monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 265. The pharmaceutical composition of claim 264, wherein the PEG moieties are branched.	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
	non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 266. The pharmaceutical composition of claim 264, wherein the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa), mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa).	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.) "As an exemplary illustration of the pegylation of an illustrative sHASEGP, PEG aldehydes, succinimides and maleimides have each been applied to conjugate PEG moieties to rHuPH20. Of these three chemistries, succinimidyl PEGs have typically been the most convenient to use in the case of rHuPH20. For example, rHuPH20 has been conjugated with exemplary succinimidyl monoPEG (mPEG) reagents including mPEG-Succinimidyl Propionates (mPEG-SPA),

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
	mPEG-Succinimidyl Butanoates (mPEG-SBA), and mPEG2-N-Hydroxylsuccinimide. These pegylated succinimidyl esters contain different length carbon backbones between the PEG group and the activated cross-linker, and either a single or branched PEG group. These differences can be used, for example, to provide for different reaction kinetics and to potentially restrict sites available for PEG attachment to rHuPH20 during the conjugation process." ('716 Application, ¶ 0814.)
Claim 278. A kit, comprising: (a) the pharmaceutical composition of claim 264; (b) at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and (c) optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex.	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 291. The pharmaceutical composition of claim 264, wherein the PEG moiety results from	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
reaction with mPEG-Succinimidyl Butanoate 30kD (mPEG-SBA (30kD)).	sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.) "As an exemplary illustration of the pegylation of an illustrative sHASEGP, PEG aldehydes, succinimides and maleimides have each been applied to conjugate PEG moieties to rHuPH20. Of these three chemistries, succinimidyl PEGs have typically been the most convenient to use in the case of rHuPH20. For example, rHuPH20 has been conjugated with exemplary succinimidyl monoPEG (mPEG) reagents including mPEG-Succinimidyl Propionates (mPEG-SPA), mPEG-Succinimidyl Butanoates (mPEG-SBA), and mPEG2-N-Hydroxylsuccinimide. These pegylated succinimidyl esters contain different length carbon backbones between the PEG group and the activated cross-linker, and either a single or branched PEG group. These differences can be used, for example, to provide for different reaction kinetics and to potentially restrict sites available for PEG attachment to rHuPH20 during the conjugation process." ('716 Application, ¶ 0814.)
Claim 292. The pharmaceutical	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
composition of claim 264 that is formulated for intravenous administration.	techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 293. The pharmaceutical composition of claim 264, wherein the pegylated hyaluronidase is soluble and active at neutral pH.	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation).

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
	Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 295. The pharmaceutical composition of claim 264 that comprises a Pegylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1.	(greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 296. The pharmaceutical composition of claim 264, wherein: the Pegylated hyaluronidase is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.	
Claim 297. The pharmaceutical composition of claim 296, wherein a hyaluronidase in the composition consists of amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 298. The pharmaceutical composition of claim 295, wherein the hyaluronidase glycoprotein is produced by expression	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
of a nucleic acid molecule that encodes amino acids 1-482 or 36-482 of SEQ ID NO:1 in a mammalian cell.	approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 300. The pharmaceutical composition of claim 264, wherein the hyaluronidase polypeptide has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4.	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units

Pending Claims of the '171 Application	Exemplary Disclosure(s) in the '716 Application
	of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)
Claim 303. The pharmaceutical composition of claim 264, wherein the hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1.	"Succinimidyl PEGs (as above) comprising either linear or branched PEGs have been conjugated to rHuPH20. Using compositions and techniques as described in the art, succinimidyl PEGs have been used to generate rHuPH20s reproducibly comprising a combination of molecules having between about three to six PEG molecules per sHASEGP. Such pegylated rHuPH20 compositions were readily purified to yield compositions having specific activities of approximately 25,000 Unit/mg protein hyaluronidase activity, and being substantially free of non-PEGylated rHuPH20 (less than 5% non-PEGylated). As is known in the art, and described for example in PEGylation references including those cited above, a variety of reagents and techniques are also available for achieving mono-disperse as opposed to poly-disperse PEG products (see, e.g., the reviews and references cited above related to site-specific monoPEGylation and site-directed PEGylation). Improvements in both pharmacokinetics and pharmacodynamics have been observed in animal models following administration of a PEGylated sHASEGP as compared to the unmodified version of the sHASEGP. For example, following intravenous administration to mice of either 1,000 Units of an unmodified rHuPH20 or 1,000 Units of rHuPH20 conjugated to PEGs having a molecular weight of approximately 40 kDa (rHuPH20-PEG40), it was observed that the serum half-life of neutral active hyaluronidase activity (PH20) in serum of mice treated with rHuPH20-PEG40 was significantly longer (16-20 fold) than that of mice treated with unmodified rHuPH20. In addition, the effectiveness of rHuPH20-PEG40 has been compared to non-PEGylated rHuPH20 in a rat stroke model. Initial results from these studies demonstrate greater effectiveness of rHuPH20-PEG40 (greater than 75% survival, versus less than 50% in controls) in rat survival 7 days post stroke-inducement." ('716 Application, ¶¶ 0815-0816.)

71. In my opinion, the disclosures of the February 23, 2005 '716 Application provides adequate written description and enablement support for each of the Pending Claims of the '171 Application, *inter alia*, (a) it discloses random PEGylation of the human hyaluronidase of 3 to 6 PEG moieties, (b) it describes succinimidyl PEGs, which conveys that random amine PEGylation is being performed, (c) it discloses that branched and linear PEGs have been generated, (d) it discloses that a pharmaceutical composition has been formulated, (e) it discloses that the composition is formulated for systemic/intravenous administration, (f) it discloses that the PEGylated human hyaluronidase is soluble and active at neutral pH, (g) it discloses improvements in pharmacokinetics and pharmacodynamics have been observed, and (h) as disclosed elsewhere in the specification, the term sHASEGP includes the specific glycosylation and amino acid SEQ IDs claimed. *See, e.g.*, '716 Application (HALOZ0000295-HALOZ0000324), Sequence listings at pp. 279-308.

B. The Claimed Invention

72. The Pending Claims are directed to pharmaceutical compositions formulated for systemic administration that contain PEGylated human-derived hyaluronidase, with three to six PEG moieties per hyaluronidase molecule.

73. Traditionally, hyaluronidases were used as pharmaceutical compositions for subcutaneous administration or local administration for its use as a spreading agent to facilitate the delivery of a therapeutic agent. '140 Bookbinder, ¶ 0051. For these subcutaneous and local applications, the short half-life of hyaluronidase is not important as it does not have a negative impact on the administration of the therapeutic, and the duration of action is sufficiently long to achieve the desired effect.

74. On the other hand, the invention of the '171 Application teaches that human-derived hyaluronidase by itself has therapeutic activity, *i.e.*, it is a pharmaceutical composition. For human-derived hyaluronidase to be used as a therapeutic, it is systemically administered, such as intravenously. In these therapeutic applications, the pharmaceutical composition comprising the human-derived hyaluronidase must have a sufficient half-life to reach its target and also retain its activity to exert a therapeutic effect. One of skill reading the '171 Application, the Pending Claim's limitations of "pharmaceutical composition," formulated for "systemic administration," and, in Claim 293, express requirements of "solubility" and "active" along with the intended utility all show that level of half-life and therapeutic efficacy are limitations of the invention of the '171 Application Pending Claims. But the amount of time that an unmodified human-derived hyaluronidase retains therapeutic levels of enzymatic activity in systemic circulation is not sufficient to achieve a non-local therapeutic effect.

75. There was no teaching or motivation in the art to modifying this enzyme for use as a therapeutic agent, as opposed to a spreading agent. Likewise, there was no teaching or motivation that human-derived hyaluronidase could be PEGylated to increase half-life sufficiently for such therapeutic uses without destroying its enzymatic activity.

76. In 2004-2005, Halozyme scientists and named inventors Louis Bookbinder, Anirban Kundu and Gregory Frost set out to make a new form of human-derived hyaluronidase for use as a therapeutic.

77. There were many unanswered questions about the mechanism of action of human-derived hyaluronidase that provided no clear approach to take.

78. After extensive research, the Halozyme inventors made the claimed invention of the '171 Application, namely, a pharmaceutical composition for systemic administration that

contained PEGylated human-derived hyaluronidase, with three to six PEG moieties per hyaluronidase molecule via random, amine-directed PEGylation via the lysine residues.

79. The inventors discovered that three to six PEG moieties achieves the maximum increase in plasma half-life afforded by PEGylation while still retaining activity such that it is useful as a therapeutic. Bookbinder Declaration, at pp. 6-7 and Fig. 2 (A1621-A1628), *see also* '171 Application, Example 21A at ¶¶ 0814-0825 (A229-A233). The inventors also demonstrated that higher levels of PEGylation exhibited reduced enzymatic activity and did not significantly increase half-life, as compared to three to six PEG moieties. *Id*. Similarly, at low levels of PEGylation, half-life was not substantially increased to result in a therapeutically active polypeptide. *Id*.

80. Example 21-A of the '171 Application teaches that the resulting PEGylated hyaluronidases were purified to yield compositions having specific activities of 25,000 units/mg hyaluronidase catalytic. '171 Application, ¶ 0816 (A230). Example 21-A further teaches that such a PEGylated hyaluronidase overcame problems associated with systemic administration of unmodified human-derived hyaluronidase that have short half-life and undesired pharmacokinetic and pharmacodynamics properties, and that PEGylation with three to six PEG moieties improved half-life 16-20 fold. '171 Application, ¶ 0817 (A230). The results in Example 21-A also confirm that this level of PEGylation is sufficient to retain activity to provide a therapeutic effect. *Id.*

C. The Pending Claims

81. I understand that a patent may include two types of claims, independent claims and dependent claims. An independent claim stands alone and includes only the limitations it recites. A dependent claim can depend from an independent claim or another dependent claim. I

understand that a dependent claim includes all the limitations that it recites in addition to all of the limitations recited in the claim from which it depends.

82. I understand that 13 claims are at issue in this litigation: Claims 264-266, 278, 291-293, 295-298, 300, and 303 of the '171 Application (A1248-A1250).

83. Claims 265, 266, 291, 292, 293, 295, 296, 300 and 303 are dependent on Claim 264 of the '171 Application.

84. Claim 297 is dependent on Claim 296, which is dependent on Claim 264 of the '171 Application.

85. Claim 298 is dependent on Claim 295, which is dependent on Claim 264 of the '171 Application.

86. Claim 264 of the '171 Application recites: "A pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein: the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule; the hyaluronidase polypeptide is a human-derived hyaluronidase; and the composition is formulated for systemic administration."

87. Claim 265 of the '171 Application recites: "The pharmaceutical composition of claim 264, wherein the PEG moieties are branched."

88. Claim 266 of the '171 Application recites: "The pharmaceutical composition of claim 264, wherein the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa), mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-

NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa)."

89. Claim 278 of the '171 Application recites: "A kit, comprising: (a) the pharmaceutical composition of claim 264; (b) at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and (c) optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex."

90. Claim 291 of the '171 Application recites: "The pharmaceutical composition of claim 264, wherein the PEG moiety results from reaction with mPEG-Succinimidyl Butanoate 30kD (mPEG-SBA (30kD))."

91. Claim 292 of the '171 Application recites: "The pharmaceutical composition of claim 264 that is formulated for intravenous administration."

92. Claim 293 of the '171 Application recites: "The pharmaceutical composition of claim 264, wherein the pegylated hyaluronidase is soluble and active at neutral pH."

93. Claim 295 of the '171 Application recites: "The pharmaceutical composition of claim 264 that comprises a Pegylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1."

94. Claim 296 of the ’171 Application recites: “The pharmaceutical composition of claim 264, wherein: the Pegylated hyaluronidase is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.”

95. Claim 297 of the ’171 Application recites: “The pharmaceutical composition of claim 296, wherein a hyaluronidase in the composition consists of amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.”

96. Claim 298 of the ’171 Application recites: “The pharmaceutical composition of claim 295, wherein the hyaluronidase glycoprotein is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 or 36-482 of SEQ ID NO:1 in a mammalian cell.”

97. Claim 300 of the ’171 Application recites: “The pharmaceutical composition of claim 264, wherein the hyaluronidase polypeptide has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4.”

98. Claim 303 of the ’171 Application recites: “The pharmaceutical composition of claim 264, wherein the hyaluronidase polypeptide consists of a sequence of amino acids that has

at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1."

99. In reaching the opinions express in this report, I have applied the knowledge of a person of ordinary skill in the art in completing my analysis of these claim terms.

VII. '140 BOOKBINDER IS NOT A PRIOR ART REFERENCE UNDER 35 U.S.C. § 102 TO THE PENDING CLAIMS OF THE '171 APPLICATION

100. The '171 Application claims priority to February 23, 2005, the filing date of the '716 Application. The '171 Application lists Gregory I. Frost, Louis H. Bookbinder, and Anirban Kundu as inventors. These are the same inventors listed on '140 Bookbinder.

101. As discussed above, each of the Pending Claims have written description and enablement support in the disclosure of the '716 Application.

102. Thus, it is my understanding that '140 Bookbinder, which was filed on March 5, 2004 and published on September 16, 2004, cannot serve as a prior art reference to the '171 Application as it published less than a year prior to February 23, 2005, and is not work of another. I further understand that the PTO asserted that it is the combination of '140 Bookbinder with Braxton or Thompson that form the obviousness combination and did not assert that Braxton or Thompson alone rendered the inventions obvious. Therefore, I do not address those references separately for obviousness.

VIII. ALTERNATIVELY, PENDING CLAIMS 264-266, 278, 291-293, 295-298, 300 and 303 OF THE '171 APPLICATION ARE NOT RENDERED OBVIOUS BY '140 BOOKBINDER, BRAXTON AND THOMPSON

103. I understand that the "test for obviousness is what the combined teachings of '140 Bookbinder, Braxton, and Thompson would have suggested to one of ordinary skill in the art." July 27, 2016 Decision on Appeal, at p. 5 (A2215).

104. In my opinion, the combination of the three identified prior art references, Braxton, Thompson and '140 Bookbinder do not render obvious the Pending Claims of the '171 Application.

105. Further, secondary considerations of non-obviousness further evidence patentability of the Pending Claims of the '171 Application, including unexpected results, long-felt but unmet need, and industry praise and recognition, and each of these factors are commensurate in scope with the Pending Claims of the '171 Application as described further in Section XII below.

A. The Differences Between the Pending Claims and The Prior Art

106. Below, I summarize some of the key information described in the three identified prior art references and explain the distinctions to the Pending Claims.

1. Braxton discloses site-specific PEGylation at cysteine residues and highlights drawbacks of utilizing multi-PEGylation at lysine residues

107. The Board agreed with the Examiner that Braxton "teach[es] and suggest[s] PEGylation of proteins to increase half-life." July 27, 2016 Decision on Appeal, at p. 6 (A2216).

108. Braxton teaches "PEGylated proteins" where PEG is attached at "***cysteine residue[s]***, which is either present in the native protein or introduced by ***site-specific mutation***." Braxton, 3:38-41 (emphasis added).

109. Braxton states that the "modified proteins produced by the method of the invention are referred to as "cysteine-PEGylated proteins." Braxton, Abstract.

110. Braxton also teaches that these site-specific cysteine-PEGylated proteins have increased half-life and decreased immunogenicity and antigenicity while retaining substantially the same level of biological activity as that of the naturally-occurring, unmodified protein. Braxton, Abstract.

111. As an initial matter, Braxton's teaching of PEG conjugation at the cysteine residues is irrelevant to the amine-directed PEG conjugation at lysine residues method used for the human-derived hyaluronidase disclosed in the '171 Application. Moreover, PEG conjugation at the native cysteine residues would be unsuitable for the instant claimed invention because 10 of the 12 cysteine residues in rHuPH20 form five disulfide bonds that are essential for its enzyme activity and the remaining two are likely necessary for binding and activity. '140 Bookbinder, ¶¶ 0044, 0565; Li *et al.*, *Importance of Glycosylation and Disulfide Bonds in Hyaluronidase Activity of Macaque Sperm Surface PH-20,* J. Andrology 23(2): 211-219 (2002) (HALOZ0000678-HALOZ0000686) ("Li 2002"). In fact, Braxton acknowledges that PEG must be attached to a cysteine amino acid within a protein, "which cysteine amino acid of the protein is not involved in a disulfide bond." Braxton, 3:44-48.

112. Thus, a skilled artisan would understand that PEG conjugation at the native cysteine residues would likely abolish biological activity by disrupting rHuPH20's structure, and as a result, not be suitable for therapeutic uses as contemplated by Braxton. *See, e.g.,* Braxton, 10:26-31 ("Chemically modified proteins, and more specifically cysteine-PEGylated proteins, suitable for therapeutic applications are produced by attaching polyethylene glycol to a cysteine residue within the protein. To obtain the desired result of a stable, biologically active compound the PEG must be attached in a specific manner.")

113. Braxton also proposes another approach of site-directed mutagenesis to add a cysteine residue at the protein's glycosylation site, but that approach would also be unsuitable for rHuPH20. Braxton, 3:50-55. Unlike most proteins, rHuPH20 is unique in that glycosylation is also essential for its enzymatic activity. '140 Bookbinder, ¶ 0045; Li 2002. Moreover, such modifications would deviate from the amino acid sequence of the claimed human-derived

hyaluronidase taking such structures out of the claims, particularly those that have a specific SEQ ID.

114. The rHuPH20 disclosed in the '171 Application differs from the exemplary protein Nexin-1 (PN-1) and proteins disclosed in Table 1A of Braxton as "Specific Exemplary Proteins" in other ways. Braxton, 12:7-47, Table 1A. For example, none of the identified proteins include an enzyme that uses a macromolecularsubstrate like rHuPH20. In other words, none of the listed proteins cleave or lyse carbohydrates like rHuPH20. In fact, the extensive list of exemplary proteins or even classes of proteins does not cover any glycoaminoglycosidases such as hyaluronidase.

115. The Board adopted the Examiner's finding that Braxton taught that the "chemically modified proteins contain at least one PEG moiety, preferably at least two PEG moieties, up to a maximum number of PEG moieties bound to the protein without abolishing activity…The ratio of PEG to protein is preferably 1:1, more preferably 2:1, even more preferably 5:1, up to a 10:1 or 40:1 ratio of PEG molecules to protein." Braxton, 12:66-13:7. As discussed above however, the chemically modified proteins of the Braxton invention relate specifically to cysteine-PEGylated proteins. And Braxton acknowledged that in order "[t]o obtain the desired result of a stable, biologically active compound the PEG must be attached in a specific manner." Braxton, 10:29-31. Thus, one of skill would not agree with the Examiner's and the Board's statement as it clearly misapprehends Braxton's disclosure.

116. Moreover, the higher ratios of PEG, *i.e.*, introduction of multiple cysteines to a protein for the purpose of PEGylation, as disclosed in Braxton, is counterproductive with the intent and goals of Braxton, namely the preservation of activity and homogeneity of the end product. Rather, as more cysteines are introduced, it is likely to lead to heterogeneous,

improperly folded, and inactive protein aggregates. Braxton is silent on the unavoidable difficulties in controlling manipulation of the newly introduced cysteines in the presence of indigenous cysteine residues for conjugation (for the former group of cysteines) and for proper disulfide formation and protein folding (for the latter). It's important to note that the goal of utilizing site-specificity is to attach one or a few PEGs at sites where they are beneficial and do not adversely affect properties of the conjugate. In contrast to lysine, cysteines are prone to disulfide formation, which in turn is essential for the proper folding and stabilization of the three dimensional protein structure.

117. Braxton also advocates increasing the molecular weight of conjugates to "30,000-40,000 MW" because Braxton's teachings focus on smaller molecular weight proteins. Braxton, 12:59-62. This is in stark contrast to rHuPH20, *i.e.*, human-derived hyaluronidase which even in its native form prior to PEGylation, is approximately 60 kDa in molecular weight.

118. In fact, I note that Braxton discourages the very method employed by Halozyme in PEGylating rHuPH20 as claimed in the '171 Application. Specifically, random, multi-PEGylation of the lysine residues on rHuPH20. Braxton teaches that PEGylating lysine residues is random and "result[s] in the production of a heterogeneous mixture of PEGylated proteins which differ in both the number and position of PEG groups attached" rendering "[s]uch mixtures of diversely modified proteins [] ***not suitable as pharmaceutical compositions***." Braxton, 2:23-34 (emphasis added). Of course, the express claim language in the '171 Application is directed to "a pharmaceutical composition," confirming how one of skill would understand Braxton to teach away from the claimed inventions because lysine conjugation is "not suitable" for pharmaceutical compositions. Braxton also notes that while there are several other methods for protein modification with PEG through free lysine residues, "each suffers from

the problems associated with partial, random modification of protein and the potential for losing activity if lysine residues are essential for biological activity." Braxton, 2:60-65; *see generally* Braxton, 2:12-65.

119. In sum, Braxton fails to disclose or suggest a pharmaceutical composition comprising a PEGylated human-derived hyaluronidase of three to six PEG moieties that is suitable for systemic administration and is soluble and active at neutral pH.

2. Thompson discloses site-specific PEGylation at cysteine residues and warns of the drawbacks of PEGylation at lysine residues

120. The Board agreed with the Examiner that Thompson "teach[es] and suggest[s] PEGylation of proteins to increase half-life." July 27, 2016 Decision on Appeal, at p. 6 (A2216). One of skill would not agree with this statement as it clearly misapprehends Thompson's disclosure.

121. Thompson teaches making a "dumbbell" conjugates of a R1-PEG-R2 structure with a bivalent PEG in-between two proteins (R1 and R2), with bifunctional PEG reagents, among which heterobifunctional PEGs are clearly preferable when R1≠R2. Thompson, 15:31-16:56. In these "dumbbell" constructs, PEG serves as a spacer, not a properties modifier, as in a typical protein PEGylation. Preparing such dumbbell constructs is not relevant to the human-derived hyaluronidase disclosed in the '171 Application.

122. More specifically, Thompson teaches PEGylating the reactive thiol moiety of a biologically active molecule such as tumor necrosis factor ("TNF") inhibitors, Interleukin-1 receptor antagonists, CR1, exon six peptide of PDGF, and the Interleukin-2 inhibitors and receptors. Thompson, 3:42-55. Thompson states that an "example of a reactive thiol is the –SH of the amino acid cysteine." Thompson, 6:42-43.

123. Thompson proposes creating "cysteine muteins" wherein a nonessential amino acid can be substituted with a cysteine or a cysteine residue can be added to the polypeptide." Thompson, 7:12-15. Further, Thompson states that "[p]otential sites for introduction of a non-native cysteine include glycosylation sites and the N or C terminus of the polypeptide." Thompson, 7:15-17.

124. This site-specific "cysteine muteins" modification approach disclosed in Thompson is unsuitable for the human-derived hyaluronidase disclosed and claimed in the '171 Application. As explained above, 10 of the 12 cysteine residues in rHuPH20 form five disulfide bonds that are essential for its enzyme activity and the remaining two are likely necessary for binding and activity. '140 Bookbinder, ¶¶ 0044; Li 2002. Thus, a skilled artisan would understand that PEG conjugation at the cysteine residues would likely abolish biological activity by disrupting rHuPH20's structure. Indeed, Thompson notes that "[m]any proteins do not have free cysteines (cysteines not involved in disulfide bonding) or any other reactive thiol group." Thompson, 6:43-45. Introducing non-native cysteine to the glycosylation sites as Thompson suggests would also be unsuitable because glycosylation is essential for rHuPH20's enzymatic activity, unlike most other proteins. '140 Bookbinder, ¶¶ 0045; Li 2002. Thompson's teaching to mono-PEGylate at the cysteine residues teaches away from the 3-6 PEGs of the instant claimed invention of the '171 Application. Moreover, deviating from the amino acid sequence of human-derived hyaluronidase by cysteine mutations would likely take the protein outside of the Pending Claims, particularly those with specific SEQ IDs.

125. Thompson also teaches PEGylation of low molecular weight proteins (TNF binding proteins and inhibitors with a molecular weight in the range of 30-40kDa). *See* Thompson, 5:50-6:21. As noted above, rHuPH20 is not a low molecular weight protein and

Thompson does not address the effects of PEGylation on higher molecular weight proteins like rHuPH20 (molecular weight ≈60 kDa).

126. Thompson promotes "site selective PEGylation of [therapeutic] proteins" as leading to "reproducibly-modified materials that gain the desirable attributes of PEGylation without the loss of activity." Thompson, 2:25-28. Thompson states that non-specific PEGylation is disadvantageous for proteins intended for therapeutic use because "the multiple species mixture that results from the use of non-specific PEGylation leads to difficulties in the preparation of a product with reproducible and characterizable properties. This non-specific PEGylation makes it difficult to evaluate therapeutics and to establish efficacy and dosing information." Thompson, 2:19-25.

127. Like Braxton, Thompson highlights the problems and drawbacks associated with non-specific PEGylation at lysine residues: "PEGylation of proteins illustrates some of the problems that have been encountered in attaching PEG to surfaces and molecules. The vast majority of PEGylating reagents react with free primary amino groups of the polypeptide. Most of these free amines are the epsilon amino group of lysine amino acid residues. Typical proteins possess a large number of lysines. Consequently, random attachment of multiple PEG molecules often occurs leading to loss of protein activity." Thompson, 2:10-18. Thus, in my opinion, a skilled artisan reading Thompson would be discouraged from using the very method employed by Halozyme in PEGylating rHuPH20 as claimed in the '171 Application.

128. The Examiner stated that an "important teaching of the '170 is that PEGylation decrease the rate of clearance from blood stream, and, up to a certain size, the rate of glomerular filtration of proteins is inversely proportional to the size of the protein. Also, '170 teaches that the ability of PEGylation to decrease clearance in generally not a function of how many PEGs

are attached to the protein, but the overall molecular weight of the conjugate, and that decreased clearance can lead to increased efficacy over the non-PEGylated material." Examiner Answer at p. 4 (A2177); *see also* Thompson, 1:59-67.

129. This teaching however, does not comport with the case of rHuPH20 as claimed in the '171 Application. Specifically, rHuPH20 is already a high molecular weight protein of 60 kDa, which is the approximate threshold of glomerular clearance. Rather than the overall molecular weight of the altered protein, the unique structure of rHuPH20 plays a critical role in clearance of the enzyme. *See, e.g.*, '140 Bookbinder, ¶ 0170-0171 ("The circulatory lifetime of glycoproteins in the blood is highly dependent on the composition and structure of its N-linked carbohydrate groups. This fact is of direct relevance for therapeutic glycoproteins that are intended to be administered parenterally."); ¶ 0455 ("The precise composition and structure of the carbohydrate chain(s) on a glycoprotein can directly influence its serum lifetime, since cells in the liver and reticuloendothelial system can bind and internalize circulating glycoproteins with specific carbohydrates."). Further, the ability of PEGylation to decrease clearance was affected by the number of PEGs attached to the rHuPH20. *See* Bookbinder Declaration (A1621-A1628).

130. The Examiner also stated that "the '170 patent teach the relationship between the rate of clearance by the kidney to the molecular weight" (Examiner Answer at p. 4, A2177), but rHuPH20 is not cleared by the kidney, and as explained above, clearance by the reticuloendothelial system (RES) is a function of the structure of rHuPH20 rather than molecular weight.

131. In sum, Thompson fails to disclose or suggest a pharmaceutical composition comprising a higher molecular weight protein such as human-derived hyaluronidase that is randomly PEGylated at the lysine residues. Thompson also fails to disclose a particular number

of PEG moieties required to increase the half-life of human-derived hyaluronidase while retaining biological activity suitable for therapeutic use. As such, Thompson also fails to disclose PEGylated human-derived hyaluronidase with 3-6 moieties.

3. '140 Bookbinder discloses rHuPH20 and many approaches to modifying this enzyme, providing no motivation to focus on PEGylation or reasonable expectation of success of achieving the PEGylated rHuPH20 claimed in the '171 Application

132. The Board agreed with the Examiner that "Bookbinder teaches all of the limitation of the claimed composition except for 'about three to six PEG moieties.'" July 27, 2016 Decision on Appeal, at p. 6 (A2216). One of skill would not agree with this statement as it misapprehends the '140 Bookbinder disclosure.

133. '140 Bookbinder teaches soluble neutral active hyaluronidases, particularly the human soluble PH-20 hyaluronidase glycoproteins (also referred to as sHASEGPs). '140 Bookbinder, ¶ 0018. Because the full length hyaluronidase is not very soluble due to a membrane domain, truncated versions are taught to create a soluble human PH-20 hyaluronidase glycoprotein. *See, e.g.*, '140 Bookbinder, ¶¶ 0067, 0079.

134. '140 Bookbinder describes general approaches/methods known in the prior art that could be applicable to modifying sHASEGPs to prolong half-life. *See, e.g.*, '140 Bookbinder, ¶ 19 ("Further provided are methods to modify the sHASEGP to prolong its half life by way of masking the protein with polyethylene glycol and posttranslational modifications to native glycosylation."); ¶¶ 0177-0184 (general information regarding PEG and known PEGylation techniques). The only prophetic examples of utilizing PEGylation are for promoting increased residence time in certain specialized local situations *that are not relevant to the claimed invention for systemic administration*. *See* '140 Bookbinder, ¶¶ 0053, 0483-0484, and

0518 (prophetic example of PEGylated sHASEGPs are envisioned for ophthalmic applications and myxedema).

135. In fact, '140 Bookbinder discloses many other modification approaches including antibodies and polymeric molecules other than PEG, including polyalkylene oxides (PAO), such as polyalkylene glycols (PAG), polyvinyl alcohol (PVA), polycarboxylates, polyvinylpyrrolidone, poly-D,L-amino acids, polyethylene-co-maleic acid anhydride, polystyrene-co-maleic acid anhydride, dextrans including carboxymethyl-dextrans, heparin, homologous albumin, celluloses, including methylcellulose, carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose carboxyethylcellulose and hydroxypropylcellulose, hydrolysates of chitosan, starches such as hydroxyethyl-starches and hydroxypropyl-starches, glycogen, agaroses and derivatives thereof, guar gum, pullulan, inulin, xanthan gum, carrageenan, pectin, alginic acid hydrolysates and bio-polymers. '140 Bookbinder, ¶ 0182; *see also* '140 Bookbinder, ¶¶ 0025 ("Chemical modifications of a sHASEGP with polymers such as polyethylene glycol and dextran are provided."); ¶ 0125 ("As used herein, an antibody conjugate refers to a conjugate in which the targeting agent is an antibody."); ¶¶ 0181-0184 (description of suitable polymeric molecules); and ¶ 0254 ("Also contemplated herein are sHASEGP polypeptide proteins, domains thereof, derivatives or analogs or fragments thereof, which are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, pegylation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand.").

136. Of the vast array of approaches, '140 Bookbinder teaches to one of skill that super-sialylation is the preferable method for increasing half-life of human-derived hyaluronidase in circulation. *See, e.g.*, '140 Bookbinder, ¶ 0022 ("Super-sialated sHASEGPs

possess greater serum half-lives compared to naturally occurring non-sialated bovine and ovine testes sHASEGPs, and are thus preferable for both enzyme stability and use as intravenous drugs."); ¶ 0049 ("Super-Sialated sHASEGP's are preferable to increase serum half-life and distribution over native hyaluronidase enzymes that lack terminal sialic acids."); ¶ 0462 ("Comparisons of super sialated sHASEGP to non-sialated bovine and ovine hyaluronidases reveal that substantially more favorable pharmacokinetics is achieved" for systemic treatment of tumors); ¶ 0495 (super sialated sHASEGP can be used for brain edemas); ¶¶ 0499-0500 (super sialated sHASEGP can be used to reduce myocardial infarcts and coronary plaques); and ¶ 0606 ("first report of the generation of a substantially sialated human sHASEGP…very valuable for both stability and to enhance serum half-life of a human sHASEGP as native sperm sHASEGP from many species lacks sialation and does not react with sialic acid specific lectins").

137. '140 Bookbinder also teaches that the glycans are necessary for human hyaluronidase activity but does not disclose why: "The studies shown herein demonstrate that human PH20 requires N-linked glycans for catalytic activity, whereas bovine and bee venom hyaluronidases remain active without such N-linked glycans. A human hyaluronidase domain devoid of N-linked moieties is catalytically inactive." '140 Bookbinder, ¶ 0020; *see also* ¶ 0045 ("N-linked glycosylation of the sHASEGP's are critical for their catalytic activity and stability…sHASEGPs are thus unique in this regard, that removal of N-linked glycosylation can result in near complete inactivation of the Hyaluronidase activity."); Example 11, pp. 151-152. Therefore, in my opinion, a skilled artisan would not know if attachment of 3-6 PEGs as claimed in the '171 Application might interfere with activity.

138. Moreover, '140 Bookbinder's lists a variety of modes of administration to "include, but are not limited to, topically, locally, intraarticularly, intracisternally, intraocularly,

peri-orbitally, intraventricularly, intrathecally, intravenously, intramuscularly, intratracheally, intraperitoneally, intradermally, subcutaneously, and by a combination of any two or more thereof" does not provide a skilled artisan with any motivation to focus on a particular method of administration. '140 Bookbinder, ¶¶ 0370-0371; *see also* ¶ 0380 ("formulations of the sHASEGP polypeptides or soluble human hyaluronidase domains thereof for use herein include those suitable for oral, rectal, topical, inhalational, buccal (e.g., sublingual), parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous), transdermal administration or any route."); and ¶ 0469 (more administration routes are described). I note that '140 Bookbinder teaches that the "most suitable route in any given case depends on the nature and severity of the condition being treated and on the nature of the particular compound that is being used." '140 Bookbinder, ¶ 0380.

139. Thus, although PEGylation was generally disclosed, it was one of many approaches suggested in '140 Bookbinder as explained above. Further, even if the PEGylation approach was considered. '140 Bookbinder teaches its use for local administration while directing super-sialylation as the method to use for systemic administration of a human-derived hyaluronidase, There is nothing in '140 Bookbinder that would have guided a skilled artisan to choose random lysine PEGylation, particularly when the state of the art was trending toward site-specific cysteine PEGylation as both Thompson and Braxton clearly illustrate. At most, '140 Bookbinder simply states that a "more directed attachment is possible in proteins containing a single lysine or cysteine," which is not the case with human-derived hyaluronidase as it contains 31 lysines and 12 cysteines. '140 Bookbinder, ¶ 0180.

140. In sum, '140 Bookbinder fails to disclose or direct POSITA to a pharmaceutical composition comprising a human-derived hyaluronidase that is randomly PEGylated with three

to six moieties for use as a pharmaceutical composition that is delivered systemically and is soluble and active at neutral pH as disclosed in the '171 Application. '140 Bookbinder also fails to disclose a particular number of PEG moieties required to increase the half-life of the systemically-administered human-derived hyaluronidase while retaining biological activity suitable for therapeutic use as disclosed in the '171 Application.

B. The PTAB Decision on Appeal improperly relied on factual findings and analysis concerning the scope and content of the prior art that do not withstand scrutiny

1. FF I. Bookbinder teaches that "[t]he invention relates to…soluble neutral active Hyaluronidase Glycoproteins (sHASEGP's)[3]…[and] sialated *[sic]* and pegylated forms of a recombinant sHASEGP to enhance stability and serum pharmacokinetics." July 27, 2016 Decision on Appeal, at p. 3 (citing Bookbinder Abstract) (A2213).

141. The full text of the latter quoted statement is "The invention further comprises sialated ***[sic]*** and pegylated forms of a recombinant sHASEGP to enhance stability and serum pharmacokinetics ***over naturally occurring slaughterhouse*** [in other words, non-human] ***enzymes***." '140 Bookbinder, Abstract (emphasis added).

142. Naturally occurring hyaluronidase enzymes from slaughterhouses (i.e., bovine and ovine) were the principle source of clinical enzyme preparation for over forty years. '140 Bookbinder, ¶ 0445. However, and as '140 Bookbinder explains, these clinical enzyme preparations lacked purity (0.5-5% purity levels) and combined with their slaughterhouse origin, left them both immunogenic to humans and a potential source of Jacob Creutzfeld disease and other bovine and ovine pathogens. *Id.* '140 Bookbinder also discloses that "[c]attle or bacterially derived hyaluronidases have also been used as a 'spreading agent' to enhance the activity of chemotherapeutics and/or the accessibility of tumors to chemotherapeutics," but that

[3] Bookbinder also indicates that "the human soluble PH-20 Hyaluronidase Glycoproteins" are included within sHASEPs. (Bookbinder ¶ 18.)

the "contaminants and non human nature of such hyaluronidases result in anaphylactic reactions." '140 Bookbinder, ¶ 0447.

143. Thus, '140 Bookbinder sought to create a soluble, neutral active form of a human-derived PH20 as that overcame these historic problems with immunogenicity. The suggestion, however, was to use super-sialylated human-derived hyaluranidase for systemic administration and PEGylated human-derived hyaluronidase for local subcutaneous uses and thus does not teach or motivate one of skill using PEGylation for a systemically administered human-derived hyaluronidase of three to six PEG moieties.

2. FF 2. Bookbinder teaches that "[m]odifications of sHASEGP to further prolong the half-life are provided. Chemical modifications of a sHASEGP with polymers such as polyethylene glycol . . . are provided." (July 27, 2016 Decision on Appeal, at p. 3 (citing '140 Bookbinder, ¶ 0025.) (A2213).

144. The full text of the latter quoted sentence is "Chemical modifications of a sHASEGP with polymers such as polyethylene glycol ***and dextran*** are provided." '140 Bookbinder, Abstract (emphasis added). It goes on to state that such uses are to shield "from removal from circulation and the immune system."

145. As explained above, '140 Bookbinder "contemplated" a variety of methods to chemically modify a sHASEGP, including polyalkylene oxides (PAO), such as polyalkylene glycols (PAG), polyvinyl alcohol (PVA), polycarboxylates, polyvinylpyrrolidone, poly-D,L-amino acids, polyethylene-co-maleic acid anhydride, polystyrene-co-maleic acid anhydride, dextrans including carboxymethyl-dextrans, heparin, homologous albumin, celluloses, including methylcellulose, carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose carboxyethylcellulose and hydroxypropylcellulose, hydrolysates of chitosan, starches such as hydroxyethyl-starches and hydroxypropyl-starches, glycogen, agaroses and derivatives thereof,

guar gum, pullulan, inulin, xanthan gum, carrageenan, pectin, alginic acid hydrolysates and bio-polymers. '140 Bookbinder, ¶ 0182. '140 Bookbinder also suggested other methods of modification such as by glycosylation, acetylation, phosphorylation, amidation, pegylation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand. '140 Bookbinder, ¶ 0254. And of the various identified approaches, '140 Bookbinder teaches that super-sialylation is the preferable method for increasing half-life of human-derived hyaluronidase in circulation. *See, e.g.*, '140 Bookbinder, ¶¶ 0022, 0049, 0462, 0606.

146. Even if the PEGylation approach was taken, the quoted statement fails to consider the requirements of the human-derived hyaluronidase with the claimed features in the Pending Claims of the '171 Application. For example, a skilled artisan would still need to consider the uncertain impact of PEGylation on specific activity, selectivity, optimal pH, circulation half-life, immunogenicity, and proper *in vivo* (tumor) biodistribution for the specifically claimed pharmaceutical composition that is to be systemically administered.

147. Moreover, the last sentence in the paragraph of the quoted statement states that "methods to link to specific functional groups such as glycosylation sites, positively charged amino acids and cysteines" are provided, and there is nothing in '140 Bookbinder that would have guided a skilled artisan to choose random lysine PEGylation over a different PEGylation approach, particularly in view of the trending art. '140 Bookbinder, ¶ 0025.

148. The quoted statement also fails to consider the human-derived hyaluronidase that is PEGylated specifically with three to six moieties as claimed in the '171 Application while achieving and maintaining the above-mentioned factors. I note that the Board and Examiner do not appear to dispute this contention. July 27, 2016 Decision on Appeal, at p. 6 (Board agreed

with the Examiner that "Bookbinder teaches all of the limitation of the claimed composition except for 'about three to six PEG moieties.'") (A2216).

3. FF 3. Bookbinder teaches that "[i]n some instances, sHASEGP's can be delivered systemically by intravenous infusion." (July 27, 2016 Decision on Appeal, at p. 4 (citing '140 Bookbinder, ¶ 0049) (A2214).

149. The quoted statement fails to appreciate that the recited paragraph 49 in '140 Bookbinder does not refer to PEGylation as the means to achieve systemic delivery of human-derived hyaluronidase by intravenous administration.

150. In fact, '140 Bookbinder expressly points to a much different solution in the same recited paragraph, namely super-sialylation. '140 Bookbinder, ¶ 0049 ("Super-Sialated sHASEGP's are preferable to increase serum half-life and distribution over native hyaluronidase enzymes that lack terminal sialic acids."). A POSITA would not understand the cited paragraph to be teaching the PEGylated human-derived hyaluronidase of the claimed invention.

4. FF 4. Bookbinder teaches that "the sHASEGP polypeptides provided herein can be used . . . in combination with a second active compound, such as a therapeutically effective agent." (July 27, 2016 Decision on Appeal, at p. 4 (citing '140 Bookbinder, ¶ 0372) (A2214).

151. The full text of the quoted sentence is "For example, the sHASEGP polypeptides provided herein can be used ***as a delivery or "spreading" agent*** in combination with a second active compound, such as a therapeutically effective agent, including, but not limited to a drug or a prodrug, to facilitate delivery of or to enhance the activity of the second active ingredient." '140 Bookbinder, ¶ 0372 (emphasis added).

152. The quoted statement fails to appreciate that the recited paragraph does not refer or discuss a PEGylated human-derived hyaluronidase, or its use in conjunction with a second active compound.

153. Further, the quoted statement and recited paragraph relates to its use as a spreading agent, to facilitate subcutaneous administration of therapeutics locally and not to systemic administration – an express claim limitation. I have read Dr. Flamion's report addressing the FF4 and rely on and incorporate that analysis as further support for my opinions here. *See* Flamion Opening Report at ¶¶ 121-122, fn. 5.

5. FF 5. The Examiner finds that Braxton teaches PEGylation of proteins that are suitable for therapeutic uses. (July 27, 2016 Decision on Appeal, at p. 4 (citing Braxton Abstract; col. 10, ll. 26-52) (A2214).

154. The quoted statement fails to appreciate that Braxton teaches site-specific PEGylation at cysteine residues which are either present in the native protein or introduced by site-specific mutations, with a preference for mono-PEGylation.

155. As discussed above in Section VIII.A.1, a skilled artisan would understand that Braxton teaches PEG conjugation at the cysteine residues which is distinct and irrelevant to the amine-directed PEGylation at the lysine residues of the human-derived hyaluronidase as claimed in the '171 Application. *See, e.g.,* Braxton, 10:26-31 ("Chemically modified proteins, and more specifically cysteine-PEGylated proteins, suitable for therapeutic applications are produced by attaching polyethylene glycol to a cysteine residue within the protein. To obtain the desired result of a stable, biologically active compound the PEG must be attached in a specific manner.") Indeed, as discussed above, a POSITA would understand that PEGylating at the indigenous cysteines in human-derived hyaluronidase would destroy the structure and thus activity of the human-derived hyaluronidase.

156. Notably, Braxton does not list glycosaminoglycosidases like hyaluronidase among the extensive list of exemplary proteins or even exemplary classes of proteins suitable for

cysteine-PEGylation. *See* Braxton, 12:7:47, Table 1A. And none of the exemplary classes of proteins, or listed enzymes themselves, cleave polysaccharides similar to hyaluronidase.

157. Rather, Braxton teaches away from the very method employed by Halozyme in PEGylating rHuPH20 as claimed in the '171 Application, specifically, random, multi-PEGylation of the lysine residues on rHuPH20. Braxton teaches that PEGylating lysine residues is random and "result[s] in the production of a heterogeneous mixture of PEGylated proteins which differ in both the number and position of PEG groups attached" rendering "[s]uch mixtures of diversely modified proteins [] ***not suitable as pharmaceutical compositions***." Braxton, 2:23-34 (emphasis added). Braxton notes that while there are several other methods for protein modification with PEG through free lysine residues, "each suffers from the problems associated with partial, random modification of protein and the potential for losing activity if lysine residues are essential for biological activity." Braxton, 2:60-65; *see generally* Braxton, 2:12-65. Of course, the claims are directed to "a pharmaceutical composition," confirming that one of skill would not understand Braxton to provide the suggestion or teaching that the Patent Office found for the hyaluronidase compositions claimed.

6. FF 6. Braxton teaches that "[t]he chemically modified proteins contain at least one PEG moiety, preferably at least two PEG moieties, up to a maximum number of PEG moieties bound to the protein without abolishing activity . . . . The ratio of PEG to protein is preferably 1:1, more preferably 2:1, even more preferably 5:1, up to a 10:1 or 40:1 ratio of PEG molecules to protein." (July 27, 2016 Decision on Appeal, at p. 4 (citing Braxton col. 12, l. 66-col. 13, l. 7) (A2214).

158. As discussed above, the chemically modified proteins of the Braxton invention relate specifically to site-specific cysteine-PEGylated proteins and is inapplicable to the random lysine PEGylated human-derived hyaluronidase as claimed in the '171 Application. As a result,

the preferable PEG ratios in the quoted statement are limited to the "chemically modified proteins" or "cysteine-PEGylated proteins" of the Braxton invention.

159. As explained above, site-specific PEGylation at the cysteine residues is different from the random lysine-directed approach used in the '171 Application. The goal of site-specificity is to attach one, or at most, a few PEGs at sites where they are beneficial and do not adversely affect properties of the conjugate. In contrast to lysine, cysteines are prone to disulfide formation, which is essential for the proper folding and stabilization of the three dimensional protein structure. Introduction of multiple free cysteines to a protein is counterproductive with the intent and goals of Braxton, namely preservation of activity and homogeneity of the product. It is likely to lead to heterogeneous, improperly folded, and inactive protein aggregates. Braxton is silent on the unavoidable difficulties in controlling manipulation of multiple newly introduced cysteines in the presence of indigenous cysteine residues, for conjugation (for the former group of cysteines) and for proper disulfide formation and protein folding (for the latter group of cysteines). One of ordinary skill in the art would readily appreciate these difficulties, as well as the fact that these difficulties exponentially increase with the introduction of each additional cysteine.

160. Importantly, Braxton acknowledged that the "actual number of PEG molecules covalently bound per chemically modified protein of the invention may vary widely depending upon the desired protein stability (e.g., serum half-life) and the protein used for chemical modification." Braxton, 12:55-59. Braxton also notes that in order "[t]o obtain the desired result of a stable, biologically active compound the PEG must be attached in a specific manner." Braxton, 10:29-31.

161. Not only does Braxton highlight the variability depending on the protein to be modified, and further, the method of PEG conjugation, Braxton's teachings only focus on smaller proteins and a smaller molecular weight range of 200 to 20,000 as opposed to the '171 Application, which discloses a PEG moiety of 30kDa, and teaches a much broader range in the molecular weight of 5kDa to 60kDa (with a focus on larger weight PEG moieties). Braxton, 12:50-51.

7. FF 7. The Examiner finds that "[a]n important teaching of [Thompson] is that PEGylation decrease[s] the rate of clearance from [the] blood stream." (July 27, 2016 Decision on Appeal, at p. 4 (citing Thompson col. 4, ll. 1-30; col. 9, ll.9-12) (A2214).

162. The Board agreed with the Examiner's finding that an "important teaching of the '170 is that PEGylation decrease the rate of clearance from blood stream, and, up to a certain size, the rate of glomerular filtration of proteins is inversely proportional to the size of the protein. Also, '170 teaches that the ability of PEGylation to decrease clearance in generally not a function of how many PEGs are attached to the protein, but the overall molecular weight of the conjugate, and that decreased clearance can lead to increased efficacy over the non-PEGylated material." Examiner Answer at p. 4 (A2177); *see also* Thompson, 1:59-67.

163. This teaching relates to small proteins, which is the focus of Thompson, and which was previously studied in detail by Knauf. *See* Knauf *et al.*, *Relationship of Effective Molecular Size to Systemic Clearance in Rats of Recombinant Interleukin-2 Chemically Modified with Water-soluble Polymers*, J. BIOL. CHEM. 263(29):15064-15070 (1988), at 15068 (HALOZ0000617-HALOZ0000623) ("Knauf 1988") ("The rapid decrease in systemic clearance rate of PEG-rIL-2 as the effective molecular size increases from 21 to approximately**70** kDa, is most likely due to a progressive exclusion of the protein from glomerular filtration, and therefore from its site of metabolism in the cells lining the proximal tubule (15,23), or other sites in the

kidney. This conclusion is partly based on the abrupt change in the slope of the curve around 70 kDa, which corresponds to the molecular weight of serum albumin, a protein which is predominantly excluded from filtration by the kidney glomerular basement membrane"). However, this teaching does not comport with the case of rHuPH20 as described in the '171 Application. Specifically, the "up to the certain size" threshold of the kidney glomerular filtration, which retains in the plasma, proteins that are the size of albumin or larger, is already met by rHuPH20, which has the same size as albumin.

164. Rather than the overall molecular weight of the altered protein, the unique structure of rHuPH20 and most likely its exposed mannose residue(s) play a critical role in clearance of the enzyme. *See, e.g.*, '140 Bookbinder, ¶ 0170-0171 ("The circulatory lifetime of glycoproteins in the blood is highly dependent on the composition and structure of its N-linked carbohydrate groups. This fact is of direct relevance for therapeutic glycoproteins that are intended to be administered parenterally."); ¶ 0455 ("The precise composition and structure of the carbohydrate chain(s) on a glycoprotein can directly influence its serum lifetime, since cells in the liver and reticuloendothelial system can bind and internalize circulating glycoproteins with specific carbohydrates."). Further, the ability of PEGylation to decrease clearance was affected by the number of PEGs attached to the protein.

165. The Examiner also stated that "the '170 patent teach the relationship between the rate of clearance by the kidney to the molecular weight" (Examiner Answer at p. 4, A2177), but rHuPH20 is not cleared by the kidney, and as explained above, clearance by the RES is a function of the structure of rHuPH20 (i.e., mannoses in glycosylation) rather than molecular weight. Specifically, due to the exposed mannose residues, rHuPH20 is now known to be most likely cleared via mannose receptor, a fact that is very consistent with its extremely fast

clearance rate for a 60 kDa (threshold of glomerular filtration) protein. As explained in the Technology Background section above (Section V.C), enzymes, such as rHuPH20, with macromolecular substrates (hyaluronan) that are cleared from circulation via the mannose receptor, are very challenging to conjugate by traditional PEGylation of amines to retain activity and to gain prolonged circulation.

166. Importantly, Thompson teaches making dumbbell conjugates with a bivalent PEG between two proteins. Thompson, 15:31-16:56. Thompson also teaches making "cysteine muteins" where a nonessential amino acid can be substituted with a cysteine or a cysteine residue can be added to the polypeptide." Thompson, 7:12-15. This is a very different approach from the traditional random lysine-directed PEGylation of the rHuPD20 claimed in the '171 Application. Further, the site-specific "cysteine muteins" modification approach to creating a dumbbell conjugate as disclosed in Thompson is not relevant for the human-derived hyaluronidase claimed in the '171 Application. I also note that PEG conjugation at the indigenous cysteine residues would break the disulfide bonds, which are essential for its enzyme activity. '140 Bookbinder, ¶¶ 0044. Moreover, Thompson's teaching to mono-PEGylate at the cysteine residues teaches away from the 3-6 PEGs of the instant claimed invention of the '171 Application.

C. No motivation to combine in making the claimed PEGylated human-derived hyaluronidase of the '171 Application

167. A skilled artisan would not have been motivated to combine '140 Bookbinder, Braxton and Thompson to develop the claimed human-derived hyaluronidase of the '171 Application. As discussed previously, the site-specific cysteine PEGylation methods taught in Braxton and Thompson are irrelevant to the different approach of random amine directed PEGylation at the lysine residues. One of skill would in fact be very concerned that native

cysteine conjugation would destroy the activity of the human-derived hyaluronidase and thus not be motivated to use the Braxton or Thompson techniques.

168. In fact, Halozyme utilized the very method, *i.e.*, random, multi-PEGylation of lysine residues, that both Braxton and Thompson stated was not preferred and even unsuitable for proteins intended for therapeutic use as pharmaceutical compositions. *See* Braxton, 2:23-34 (PEGylating lysine residues is random and "result[s] in the production of a heterogeneous mixture of PEGylated proteins which differ in both the number and position of PEG groups attached" rendering "[s]uch mixtures of diversely modified proteins [] not suitable as pharmaceutical compositions."); Thompson, 2:19-25 (non-specific PEGylation is not preferable for proteins intended for therapeutic use because "the multiple species mixture that results from the use of non-specific PEGylation leads to difficulties in the preparation of a product with reproducible and characterizable properties. This non-specific PEGylation makes it difficult to evaluate therapeutics and to establish efficacy and dosing information.").

D. No reasonable expectation of success of achieving the claimed PEGylated human-derived hyaluronidase of the '171 Application

1. Braxton (and Thompson) teach site-specific PEG conjugation to cysteine residues whereas the rHuPH20 claimed in the '171 Application utilizes amine-directed PEG conjugation to lysine residues.

169. The Board "agree[d] with the Examiner's finding that determining the optimum number or range of PEG moieties per hyaluronidase molecule would have been a matter of routine optimization for a person of ordinary skill in the art." July 27, 2016 Decision on Appeal, at p. 7 (A2217). According to the Board, this is based on the factual findings that "Braxton teaches the addition of one or more PEG moieties 'without abolishing activity' (FF6), and that it

"also teaches 5 PEG moieties to 1 protein molecule, which is within the range of 'about three to six' claimed by Appellants. (*Id.*)"

170. I disagree for several reasons. First, Braxton's teachings relate to smaller proteins that are suitable for cysteine modification "without abolishing activity." This is in stark contrast to the human-derived hyaluronidase claimed in the '171 Application, a large enzyme that was PEGylated via random lysine PEGylation. Second, Braxton's disclosure of PEG ratios is similarly inapplicable to the claimed PEGylated human-derived hyaluronidase because the disclosed PEG ratios using Braxton's cysteine conjugation teachings would likely result in abolished, or greatly diminished enzymatic activity making it unsuitable for use as a pharmaceutical composition as claimed in the '171 Application.

171. While '140 Bookbinder postulates that there may be a limited number of free cysteines available for conjugation, it later teaches that most, if not all, cysteines in human PH20 are essential for its enzyme activity. '140 Bookbinder, ¶¶ 43, 565; Li 2002. Similarly, introducing cysteines via site-directed mutations at glycosylation sites also leads to loss of enzymatic activity. *See, e.g.*, '140 Bookbinder, ¶¶ 20, 45; Li 2002. Thus, there would be no reasonable expectation of success in achieving the claimed PEGylated human-derived hyaluronidase using cysteine PEGylation in any ratio, much less using random lysine PEGylation when both Braxton and Thompson argue against such approach because it was known to cause large activity losses making it unsuitable for use as a pharmaceutical composition.

172. Even if one were to accept that the Braxton approach could theoretically be applicable to the rHuPH20 claimed in the '171 Application, which I do not, there is nothing routine and obvious in going through the sequence of rHuPH20, a 60 kDa protein, identifying

possible sites for mutations based on molecular modeling and considerations related to preservation of activity and prolongation of in vivo circulation, making these mutants, and finally, testing the resulting conjugates for activity and pharmacokinetics. I note that three-dimensional structure of rHuPH20 was unknown at the time of filing, and to the best of my knowledge, is still unknown making it even more difficult to conduct site-specific mutations. I understand Dr. Flamion's opinions are consistent with my understanding as well. *See* Flamion Opening Report, Section IV.C. In my opinion, this would not be a routine experiment or mere optimization, but rather, a major R&D program.

2. Modification of proteins is highly protein specific and what is taught for modifying one protein may not be applicable to another protein

173. The Board also stated that "a person of ordinary skill in the art would have been motivated to find an optimum number (range) of PEG moieties, and we find the Bookbinder Declaration to reflect the type of routine experimentation that a person of skill in the art would have undertaken to determine an optimum range of PEG moieties given the teachings of the prior art." July 27, 2016 Decision on Appeal, at p. 7 (A2217).

174. '140 Bookbinder discloses many methods of modifying a sHASEGP besides PEGylation. '140 Bookbinder, ¶¶ 0022, 0049, 0462, 0606. When '140 Bookbinder is read as a whole, there simply is no motivation to select PEGylation over other disclosed modification methods. In fact, '140 Bookbinder suggests that super-sialylation is the preferred method.

175. Even if PEGylation was the chosen method, a skilled artisan would still need to consider how PEGylation might affect the specific activity, selectivity, optimal pH, half-life, and proper *in vivo* (tumor) biodistribution for the specifically claimed rHuPH20 of the '171 Application. The art, including '140 Bookbinder, did not teach or disclose a PEGylation method

that maintained specific activity and selectivity of rHuPH20, much less a motivation to find the optimum number of PEG moieties, 3-6 PEGs as claimed in the '171 Application.

176. For example, it was known that PEGylation usually reduces the activity of enzymes. As discussed above in the Background Technology Section (*supra* at Section V.C), this is particularly true for enzymes that have macromolecular substrates, such as rHuPH20. Studies have shown that for PEG-enzymes of this type, as the size of the substrate increases, enzymatic activity decreases. For example, PEGylated sphingomyelinase retained ability to hydrolyze low molecular weight substrate as well as the lipid, sphingomyelin (SM), present in micelles. However, in contrast to the parent enzyme, this activity was significantly decreased when SM was formulated in liposomes (approximately ten-fold larger nanoparticles than micelles), and completely abolished against bovine erythrocyte cell membrane SM (cells are approximately ten-fold larger compared to liposomes). *See, e.g.*, Matsuyama 1992, Table 1 at p. 2481. Another example of such enzyme studied in my lab was lysozyme. Attachment of even one PEG chain completely abolished its peptidoglycan cell-wall lysing activity in a *Micrococcus Luteus* assay. Zalipsky 2007; *see also* Zalipsky 1995, Table 2 at p.165 (discusses relationship between substrate size and PEGylation). All these precedents generally suggest that the larger the substrate, the lower the chances for its PEGylated enzyme to retain activity. As such, in the case of the PEGylated human-derived hyaluronidase claimed in the '171 Application that has a substrate hyaluronan that measures in the millions of Daltons (with a polymer length of 2-25μm), the successful conjugation with retention of enzymatic activity and improved *in vivo* circulation was highly unpredictable. Toole, *Hyaluronan: From Extracellular Glue to Pericellular Cue*, NATURE REVIEWS 4:528-539 (2004) (HALOZ0000767-HALOZ0000778) ("Toole 2004").

177. Enzyme stability can also be influenced by conjugation, *e.g.*, sialylation. Orkin and Toole, *Chick Embryo Fibroblasts Produce Two Forms of Hyaluronidase,* J CELL BIOL. 85:248-57 (1980) (HALOZ0000330-HALOZ0000339) ("Orkin 1980"). Thus, the effects of PEGylation on stability would need to be assessed.

178. Circulating hyaluronidases interact with numerous inhibitors of different types. Mio and Stern, *Inhibitors of the hyaluronidases,* MATRIX BIOLOGY 21:31-37 (2002) (HALOZ0000687-HALOZ0000693) ("Mio 2002"). It was not known whether, or the degree to which, PEGylated human-derived hyaluronidase would be subject to inhibition in the circulation. It was also not known how to increase half-life to overcome RES clearance and interactions with potential inhibitors in the blood without creating toxicity in the body.

179. The effects of PEGylation on the recognition of rHuPH20 glycan moieties by mannose receptors on dendritic, liver endothelial, and Kupffer cells would also be critical since this would determine the route and speed of clearance.

180. PEGylation can also shift the optimal pH, a fairly common phenomena for PEGylating enzymes. This is because PEGylation typically changes the enzyme surface charge, which in turn, impacts the isoelectric point and pH optimum of the enzyme. PEGylation can also impact the polarity of the enzyme at the attachment sites, which may influence its affinity towards substrates or receptors. *See generally* Zalipsky 1992.

181. Thus, a skilled artisan would not have had any reasonable expectation of success in making the claimed PEGylated human-derived hyaluronidase with 3-6 PEG moieties while retaining activity upon systemic administration for therapeutic use, such as for treatment of tumors – the utility of the claimed pharmaceutical composition.

3. Trend was for mono-PEGylation and site-specific PEGylation for a human recombinant protein where the substrate was a large molecule

182. The preference in the art in PEGylating proteins with macromolecular receptors or substrates was toward mono-PEGylation and site-specific conjugation of PEG so the receptor binding ability was maintained, as both Braxton and Thompson taught. *See, e.g.*, Turecek 2016, Veronese 2005, Fishburn 2007, Kinstler *et al.*, *Mono-N-terminal poly(ethylene glycol)–protein conjugates*, ADV. DRUG. DEL. REV. 54:477-485 (2002) (HALOZ0000694-HALOZ0000702) ("Kinstler 2002"). As such, a skilled artisan would have had no reasonable expectation of success in attempting to make the claimed 3-6 PEG human-derived hyaluronidase using random lysine PEGylation because based on the precedents, it was reasonable to expect that PEGylation would cause a loss of large substrate activity and/or specificity. *See, e.g.*, Zalipsky 1995. I also emphasize that an enzyme that acts on a large substrate is much more challenging to PEGylate than an enzyme that acts on small substrates because it becomes much more unpredictable as to whether activity for the large substrate can be maintained.

183. The truncated form of claimed human-derived hyaluronidase has 31 lysine residues. In my opinion, it is difficult to predict which lysines are PEGylated from the primary amino acid sequence and even with a crystal structure (I understand that one has not been elucidated for rHuPH20 even as of today), a skilled artisan could only guess which lysines will be PEGylated. I understand Dr. Flamion's opinions are consistent with my understanding as well. *See* Flamion Opening Report, Section IV.C.

184. In my opinion, achieving the claimed PEGylated human-derived hyaluronidase for systemic application that preserves its activity for macromolecular substrates and pH optimum is an unexpected result and not a matter of routine optimization for a person of ordinary skill in the art.

E. Pending Claim 264 of the '171 Application is not rendered obvious by Bookbinder, Braxton and Thompson

185. The Board affirmed the Examiner's conclusion that Claim 264 would have been obvious to a person of ordinary skill in the art in February 2005 over Braxton, Thompson and '140 Bookbinder. July 27, 2016 Decision on Appeal, at p. 5 (A2215). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 264 of the '171 Application

186. '140 Bookbinder does not disclose a pharmaceutical composition formulated for systemic administration comprising a PEGylated human-derived hyaluronidase with three to six PEG moieties. A skilled artisan when reading '140 Bookbinder as a whole, would not understand that '140 Bookbinder teaches that when human-derived hyaluronidase is used as a therapeutic for systemic administration, half-life must be increased in a manner that does not abolish its enzymatic activity. '140 Bookbinder does not disclose this problem to be solved, nor does it teach or suggest a solution.

187. Braxton does not cure the deficiencies in the teachings of '140 Bookbinder. Likewise, Thompson does not cure the deficiencies either. Neither of these references can be used to show that a skilled artisan would have routinely optimized the PEGylation of the claimed human-derived hyaluronidase as the Board states because Braxton and Thompson are directed to cysteine PEGylation via naturally occurring cysteines or site-directed mutation of cysteines. However, as explained previously, site-specific cysteine PEGylation was not the methodology used by the inventors, and as such, a skilled artisan could not have routinely optimized using cysteine PEGylation. Further, site-specific PEGylation at native cysteine residues would abolish

the PEGylated human-derived hyaluronidase's activity, making it unsuitable for use as a pharmaceutical composition formulated for systemic administration.

188. For the reasons set forth in this section and Section VIII.A-D, the combined teachings of '140 Bookbinder, Braxton and Thompson do not disclose a "pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein: the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule; the hyaluronidase polypeptide is a human-derived hyaluronidase; and the composition is formulated for systemic administration" as required by Pending Claim 264.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 264 of the '171 Application

189. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 264 of the '171 Application.

190. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 264.

F. Pending Claim 265 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

191. The Board affirmed the Examiner's rejection of Pending Claim 265, on the basis that Appellant argued that Pending Claim 265 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 265. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. ’140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 265 of the ’171 Application

192. Pending Claim 265 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 265 further require that the PEG moieties are branched.

193. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 265 is not taught or suggested by the combined teachings of ’140 Bookbinder, Braxton and Thompson.

194. Moreover, branched PEGs are known to convey more protein surface shielding compared to the linear analogs. Veronese *et al.*, *Branched and linear poly (ethylene glycol): influence of the polymer structure on enzymological, pharmacokinetic, and immunological properties of protein conjugates*, J. BIOACTIVE COMPATIBLE POLYM. 12:196-207 (1997) (HALOZ0000598-HALOZ0000609) (“Veronese 1997”). Branched PEGs are discussed in the specification of ’171 Application (p. 67, 68) and further enabled in Examples 21, 21A (p. 224-227). In my opinion, rHuPH20 conjugated with branched PEG while retaining hyaluronidase activity is surprising, perhaps even more so than its linear PEG counterpart(s). None of this is suggested by the combined teachings of ’140 Bookbinder, Braxton and Thompson.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 265 of the ’171 Application

195. A skilled artisan would not have been motivated to combine the teachings of ’140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 265 of the '171 Application.

196. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 265.

G. Pending Claim 266 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

197. The Board affirmed the Examiner's rejection of Pending Claim 265, on the basis that Appellant argued that Pending Claim 266 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 266. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 266 of the '171 Application

198. Pending Claim 266 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 266 further require that the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa), mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa).

199. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 266 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

200. Moreover, all of the PEG reagents identified in Claim 266 are used for amine-directed PEGylation approaches. As such, these PEG reagents would be inapplicable to Braxton and Thompson, both of which teach cysteine PEGylation.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 266 of the '171 Application

201. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 266 of the '171 Application.

202. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 266.

H. Pending Claim 278 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

203. The Board affirmed the Examiner's conclusion that Claim 278 would have been obvious to a person of ordinary skill in the art in February 2005 over Braxton, Thompson and '140 Bookbinder. July 27, 2016 Decision on Appeal, at pp. 7-8 (A2217-A2218). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 278 of the '171 Application

204. The kit of Pending Claim 278 includes every limitation of Pending Claim 264. Accordingly, for at least the reasons discussed with respect to Pending Claim 264, Pending

Claim 278 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

205. The kit of Pending Claim 278 further includes at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex.

206. '140 Bookbinder does not disclose such kit. Rather, the kits '140 Bookbinder teaches contain a hyaluronidase and substrate of the hyaluronidase to be assayed, reagents for detecting proteolysis of the substrate, and instructions for performing the assay. *See, e.g.*, '140 Bookbinder, ¶ 0285. A skilled artisan when reading '140 Bookbinder as a whole, would not understand that '140 Bookbinder teaches a kit comprising a PEGylated human-derived hyaluronidase with three to six PEG moieties and a therapeutic substance or molecule.

207. The Board's finding that "Bookbinder also teaches the use of its hyaluronidase polypeptides 'in combination with a second active compound, such as a therapeutically effective agent'" is misplaced. July 27, 2016 Decision on Appeal, at p. 8 (citing FF 4). As explained above, the quoted statement from '140 Bookbinder and recited paragraph relates to subcutaneous administration for use as a "spreading agent" to facilitate subcutaneous administration of therapeutics. I have read Dr. Flamion's report addressing the FF4 and rely on and incorporate that analysis as further support for my opinions here. Flamion Opening Report at ¶¶ 121-122, fn. 5.

208. Braxton does not cure the deficiencies in the teachings of '140 Bookbinder. Likewise, Thompson does not cure the deficiencies either. Neither of these references provides any teaching or even mention of kits. Both references also do not teach or mention a

hyaluronidase, much less a PEGylated human-derived hyaluronidase with three to six PEG moieties and a therapeutic substance or molecule.

209. For the reasons set forth in this section and Section VIII.A-B, the combined teachings of '140 Bookbinder, Braxton and Thompson do not disclose a "kit, comprising: (a) the pharmaceutical composition of claim 264; (b) at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and (c) optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex." as required by Pending Claim 278.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 278 of the '171 Application

210. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 278 of the '171 Application.

211. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 278.

I. Pending Claim 291 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

212. The Board affirmed the Examiner's conclusion that Claim 291 would have been obvious to a person of ordinary skill in the art in February 2005 over Braxton, Thompson and '140 Bookbinder. July 27, 2016 Decision on Appeal, at pp. 8-9 (A2218-A2219). I disagree with this finding for the reasons set forth below. Specifically, the Board noted that "while Appellants argue that '[t]here is no mention of any reaction including mPEG-Succinimidyl Butanoate 30kD

(mPEG-SBA (30kD))' in the cited art, Appellants make no argument that the PEG moiety (product) resulting from the recited reaction (process) is patentably distinct from a PEG moiety (product) of the prior art." *Id.*

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 291 of the '171 Application

213. The pharmaceutical composition of Pending Claim 291 includes every limitation of Pending Claim 264. Accordingly, for at least the reasons discussed with respect to Pending Claim 264, Pending Claim 291 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

214. The pharmaceutical composition of Pending Claim 291 further requires that the PEG moiety results from reaction with mPEG-Succinimidyl Butanoate 30kD (mPEG-SBA (30kD)).

215. '140 Bookbinder, Braxton and Thompson do not disclose a reaction with mPEG-SBA (30kD) that results in the PEG moiety of the claimed pharmaceutical composition of Pending Claim 264, namely a PEGylated human-derived hyaluronidase with three to six PEG moieties. A skilled artisan when reading '140 Bookbinder, Braxton and Thompson would understand that the PEG moiety resulting from the recited reaction of Pending Claim 291 is distinct from a PEG moiety of '140 Bookbinder, Braxton or Thompson.

216. For the reasons set forth in this section and Section VIII.A-B, the combined teachings of '140 Bookbinder, Braxton and Thompson do not disclose the "pharmaceutical composition of claim 264, wherein the PEG moiety results from reaction with mPEG-Succinimidyl Butanoate 30kD (mPEG-SBA (30kD))" as required by Pending Claim 291.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 291 of the '171 Application

217. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 291 of the '171 Application.

218. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 291.

J. Pending Claim 292 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

219. The Board affirmed the Examiner's rejection of Pending Claim 292, on the basis that Appellant argued that Pending Claim 292 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 292. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 292 of the '171 Application

220. Pending Claim 292 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 292 further requires that it is formulated for intravenous administration.

221. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 292 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

222. Both Braxton and Thompson belittle traditional random amino group-directed PEGylation that was used in the '171 Application, even referring to it as unsuitable for pharmaceutical compositions. In my opinion, only the '171 Application discusses and focuses on intravenous applications according to the Pending Claim 292.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 292 of the '171 Application

223. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 292 of the '171 Application.

224. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 292.

K. Pending Claim 293 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

225. The Board affirmed the Examiner's rejection of Pending Claim 293, on the basis that Appellant argued that Pending Claim 293 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 293. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 293 of the '171 Application

226. Pending Claim 293 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 293 further requires that the PEGylated hyaluronidase is soluble and active at neutral pH.

227. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 293 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 293 of the '171 Application

228. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 293 of the '171 Application.

229. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 293.

L. Pending Claim 295 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

230. The Board affirmed the Examiner's rejection of Pending Claim 295, on the basis that Appellant argued that Pending Claim 295 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 295. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 295 of the '171 Application

231. Pending Claim 295 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 295 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide,

wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1.

232. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 295 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

233. Pending Claim 295 is directed to a particular species of PEGylated human-derived hyaluronidase that is exemplified in the '171 Application.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 295 of the '171 Application

234. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 295 of the '171 Application.

235. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 295.

M. Pending Claim 296 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

236. The Board affirmed the Examiner's rejection of Pending Claim 296, on the basis that Appellant argued that Pending Claim 296 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no

other arguments in response to the rejection of Pending Claim 296. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 296 of the '171 Application

237. Pending Claim 296 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 296 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

238. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 296 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

239. Pending Claim 296 is directed to a particular species of PEGylated human-derived hyaluronidase that is exemplified in the '171 Application.

240. Further, Braxton and Thompson do not disclose a PEGylated human-derived hyaluronidase, much less its amino acid sequence.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 296 of the '171 Application

241. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 296 of the '171 Application.

242. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 296.

N. Pending Claim 297 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

243. The Board affirmed the Examiner's rejection of Pending Claim 297, on the basis that Appellant argued that Pending Claim 297 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 297. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 297 of the '171 Application

244. Pending Claim 297 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 297 further requires a human-derived hyaluronidase in the composition consists of amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

245. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 297 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

246. Pending Claim 297 is directed to a particular species of PEGylated human-derived hyaluronidase that is exemplified in the '171 Application.

247. Further, Braxton and Thompson do not disclose a PEGylated human-derived hyaluronidase, much less its amino acid sequence.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 297 of the '171 Application

248. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 297 of the '171 Application.

249. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable success in making the invention recited in Pending Claim 297.

O. Pending Claim 298 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

250. The Board affirmed the Examiner's rejection of Pending Claim 298, on the basis that Appellant argued that Pending Claim 298 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 298. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 298 of the '171 Application

251. Pending Claim 298 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 298 further

requires a hyaluronidase glycoprotein that is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 or 36-482 of SEQ ID NO:1 in a mammalian cell.

252. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 298 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

253. Pending Claim 298 is directed to a particular species of PEGylated human-derived hyaluronidase that is exemplified in the '171 Application.

254. Further, Braxton and Thompson do not disclose a PEGylated human-derived hyaluronidase, much less its amino acid sequence, or one that is expressed in a mammalian cell.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 298 of the '171 Application

255. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 298 of the '171 Application.

256. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable expectation of success in making the invention recited in Pending Claim 298.

P. Pending Claim 300 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

257. The Board affirmed the Examiner's rejection of Pending Claim 300, on the basis that Appellant argued that Pending Claim 300 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no

other arguments in response to the rejection of Pending Claim 300. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 300 of the '171 Application

258. Pending Claim 300 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 300 further requires a hyaluronidase polypeptide that has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4.

259. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 300 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

260. Pending Claim 300 is directed to a particular species of PEGylated human-derived human-derived hyaluronidase that is exemplified in the '171 Application.

261. Further, Braxton and Thompson do not disclose a PEGylated human-derived hyaluronidase, much less its amino acid sequence.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 300 of the '171 Application

262. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 300 of the '171 Application.

263. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable expectation of success in making the invention recited in Pending Claim 300.

Q. Pending Claim 303 of the '171 Application is not rendered obvious by '140 Bookbinder, Braxton and Thompson

264. The Board affirmed the Examiner's rejection of Pending Claim 303, on the basis that Appellant argued that Pending Claim 303 depends (or ultimately depends) on Pending Claim 264 and relied on the same arguments advanced with regard to Pending Claim 264, and raised no other arguments in response to the rejection of Pending Claim 303. July 27, 2016 Decision on Appeal, at p. 9 (A2219). I disagree with this finding for the reasons set forth below.

1. '140 Bookbinder, Braxton and Thompson fail to disclose each and every element of Pending Claim 303 of the '171 Application

265. Pending Claim 303 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 303 further requires a hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1.

266. For at least the reasons discussed with respect to Pending Claim 264, Pending Claim 303 is not taught or suggested by the combined teachings of '140 Bookbinder, Braxton and Thompson.

267. Pending Claim 303 is directed to a particular species of PEGylated human-derived human-derived hyaluronidase that is exemplified in the '171 Application.

268. Further, Braxton and Thompson do not disclose a PEGylated human-derived hyaluronidase, much less its amino acid sequence.

2. A skilled artisan would not have been motivated to develop the invention recited in Pending Claim 303 of the '171 Application

269. A skilled artisan would not have been motivated to combine the teachings of '140 Bookbinder, Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase for the same reasons discussed previously in Section VIII.C.

3. A skilled artisan would not have had a reasonable expectation of success of achieving the invention recited in Pending Claim 303 of the '171 Application.

270. For at least the reasons described previously in Section VIII.D, a skilled artisan would not have a reasonable expectation of success in making the invention recited in Pending Claim 303.

IX. PENDING CLAIMS 264-266, 278, 291-293, 295-298, 300 AND 303 OF THE '171 APPLICATION ARE NOT OBVIOUS VARIANTS OF CLAIMS 9 AND 10 OF U.S. PATENT NO. 7,767,429 IN VIEW OF BRAXTON AND THOMPSON

271. I understand that if the rejection of the Pending Claims under 35 U.S.C. § 103(a) is obviated, the rejections for obviousness-type double patenting over Claims 9 and 10 of the U.S. Patent No. 7,767,429 (the "'429 Patent") (A1719) in view of Braxton and Thompson must also be obviated for the same reasons, since the Pending Claims cannot encompass obvious variants of the subject matter of the prior patents.

272. The Board agreed with the Examiner's obviousness-type double patenting rejection of Pending Claim 264 based on the finding that Claims 9 and 10 are directed to a hyaluronidase glycoprotein modified with a PEG polymer, and Braxton and Thompson teach three to six moieties. July 27, 2016 Decision on Appeal, at p. 10 (A2220). The Examiner stated that "[b]ased on the teaching of both [Braxton and Thompson] …it would have been obvious to

one of ordinary skill in the art at the time of invention to optimize the PEGylation reaction for longest possible half-life and maximum activity." Examiner Answer, at p. 5 (A2178). The Examiner further incorporated the rejections under 35 U.S.C. § 103(a). *Id.* I disagree with this finding for the reasons set forth below.

273. In my opinion, secondary considerations of non-obviousness further evidence patentability of the Pending Claims of the '171 Application, including unexpected results, long-felt but unmet need, and industry praise and recognition, and each of these factors are commensurate in scope with the Pending Claims of the '171 Application as described further in Section XII below.

A. Pending Claim 264 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

274. In my opinion, Pending Claim 264 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 264 of the '171 Application is different from Claims 9 and 10 of the '429 Patent

275. Below is a chart that compares Pending Claim 264 of the '171 Application with the earlier issued Claims 9 (or 10) of the '429 Patent:

Pending Claim 264, '171 Application	Claim 9, '429 Patent	Claim 10, '429 Patent
264. A pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein:	9. The hyaluronidase glycoprotein of claim 7, wherein the hyaluronidase glycoprotein is modified with a polymer.	10. The hyaluronidase glycoprotein of claim 9, wherein the polymer is PEG or dextran. 9. The hyaluronidase glycoprotein of claim 7, wherein the hyaluronidase glycoprotein is modified with a polymer.
the hyaluronidase contains		

about three to six PEG moieties per hyaluronidase molecule		
the hyaluronidase polypeptide is a human-derived hyaluronidase	7. A substantially purified hyaluronidase glycoprotein, wherein the hyaluronidase glycoprotein: is soluble; is neutral active; contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the polypeptide; and consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 set forth in SEQ ID NO:1 or contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino-acid substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.	7. A substantially purified hyaluronidase glycoprotein, wherein the hyaluronidase glycoprotein: is soluble; is neutral active; contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the polypeptide; and consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 set forth in SEQ ID NO:1 or contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino-acid substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.
and the composition is formulated for systemic administration		

276. The plain text above illustrates the distinct nature of the claims.

277. A first distinction is that Pending Claim 264 requires a pharmaceutical composition…in a pharmaceutically acceptable carrier" whereas Claims 9 and 10 do not recite any such limitation.

278. A second distinction is that Pending Claim 264 requires a "hyaluronidase [that] contains about three to six PEG moieties per hyaluronidase molecule" whereas Claims 9 and 10 do not recite any such limitation.

279. A third distinction is that Pending Claim 264 requires that "the composition is formulated for systemic administration" whereas Claims 9 and 10 do not recite any such limitation.

280. In my opinion, one of ordinary skill would not understand that Claims 9 and 10 render obvious the claimed pharmaceutical composition formulated for systemic administration comprising a human-derived hyaluronidase that contains three to six PEG moieties per molecule. The claimed human-derived hyaluronidase contains many residues that could potentially be PEGylated, and as discussed above there are many additional variables that may lead to an uncertain outcome. For example, one of ordinary skill would not know whether 3-6 PEGs would retain sufficient activity and circulatory half-life to make it suitable for use as a pharmaceutical composition formulated for systemic administration as claimed in the '171 Application.

2. Pending Claim 264 of the '171 Application is patentably distinct from Claims 9 and 10 of the '429 Patent in view of Braxton and Thompson

281. These claim differences render the claims patentably distinct, and the Board's decision upholding the Examiner's rejections for obviousness-type double-patenting in view of Braxton and Thompson erroneously relied on, and failed to properly consider that Braxton and Thompson, both teach distinct site-specific cysteine PEGylation approaches in direct contrast to the random lysine-directed PEGylation approach practiced in the '171 Application. Further, Thompson teaches dumbbell conjugates, a completely different technology that is irrelevant to the PEGylated human-derived hyaluronidase claimed in the '171 Application.

282. Also, PEGylation at native cysteine residues as the method to "optimize" the PEGylation reaction in any disclosed PEG ratio by Braxton to increase half-life and activity, would actually result in abolishing the enzymatic activity of the claimed human-derived hyaluronidase of Pending Claim 264 rendering it unsuitable for use as a therapeutic for systemic administration.

283. The claimed human-derived hyaluronidase of Pending Claim 264 is a high molecular weight enzyme acting on a macromolecular substrate, and distinct from the smaller proteins disclosed in Braxton and Thompson. I note that Braxton acknowledged that the "actual number of PEG molecules covalently bound per chemically modified protein of the invention may vary widely depending upon the desired protein stability (e.g., serum half-life) and the protein used for chemical modification." Braxton, 12:55-59.

284. Moreover, Braxton and Thompson's preference for mono-PEGylation at the cysteine residues teach away from the three to six PEG moieties as required in Pending Claim 264. Indeed, both Braxton and Thompson teach away from using the random, multi-PEGylation of lysine residues stating that such approach often leads to loss of activity and high composition heterogeneity making the conjugates unsuitable for pharmaceutical compositions.

285. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

B. Pending Claim 265 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

286. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 265 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent

287. Pending Claim 265 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 265 further requires that the PEG moieties are branched.

288. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 265 is distinct from Claims 9 and 10 of the ’429 Patent.

289. A further distinction is that Pending Claim 265 also requires that the PEG moieties are branched whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 265 of the ’171 Application is patentably distinct from Claims 9 and 10 of the ’429 Patent in view of Braxton and Thompson

290. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

C. Pending Claim 266 of the ’171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

291. In my opinion, Pending Claim 266 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 266 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent

292. Pending Claim 266 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 266 further requires that the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa),

mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa).

293. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 266 is distinct from Claims 9 and 10 of the ’429 Patent.

294. A further distinction is that Pending Claim 266 also requires that the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa), mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa) whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 266 of the ’171 Application is patentably distinct from Claims 9 and 10 of the ’429 Patent in view of Braxton and Thompson

295. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

D. Pending Claim 278 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

296. In my opinion, Pending Claim 278 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 278 of the '171 Application is different from Claims 9 and 10 of the '429 Patent

297. The kit of Pending Claim 278 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. The kit of Pending Claim 278 further includes at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex.

298. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 278 is distinct from Claims 9 and 10 of the '429 Patent.

299. A further distinction is that Pending Claim 278 also requires that the kit includes at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 278 of the '171 Application is patentably distinct from Claims 9 and 10 of the '429 Patent in view of Braxton and Thompson

300. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

E. Pending Claim 291 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

301. In my opinion, Pending Claim 291 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 291 of the '171 Application is different from Claims 9 and 10 of the '429 Patent

302. Pending Claim 291 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 291 further requires that the PEG moiety results from reaction with mPEG-Succinimidyl Butanoate 30kD (mPEG-SBA (30kD)).

303. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 291 is distinct from Claims 9 and 10 of the '429 Patent.

304. A further distinction is that Pending Claim 291 also requires that the PEG moiety results from reaction with mPEG-SBA (30kD) whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 291 of the '171 Application is patentably distinct from Claims 9 and 10 of the '429 Patent in view of Braxton and Thompson

305. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

F. Pending Claim 292 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

306. In my opinion, Pending Claim 292 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 292 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent

307. Pending Claim 292 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 292 further requires that it is formulated for intravenous administration.

308. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 265 is distinct from Claims 9 and 10 of the ’429 Patent.

309. A further distinction is that Pending Claim 292 also requires that it is formulated for intravenous administration whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 292 of the ’171 Application is patentably distinct from Claims 9 and 10 of the ’429 Patent in view of Braxton and Thompson

310. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

G. Pending Claim 293 of the ’171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

311. In my opinion, Pending Claim 293 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 293 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent

312. Pending Claim 293 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 293 further requires that the PEGylated hyaluronidase is soluble and active at neutral pH.

313. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 265 is distinct from Claims 9 and 10 of the ’429 Patent.

314. A further distinction is that Pending Claim 293 also requires that the PEGylated hyaluronidase is soluble and active at neutral pH whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 293 of the ’171 Application is patentably distinct from Claims 9 and 10 of the ’429 Patent in view of Braxton and Thompson

315. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

H. Pending Claim 295 of the ’171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

316. In my opinion, Pending Claim 295 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 295 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent

317. Pending Claim 295 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 295 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1.

318. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 295 is distinct from Claims 9 and 10 of the ’429 Patent.

319. A further distinction is that Pending Claim 295 also requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1 whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 295 of the ’171 Application is patentably distinct from Claims 9 and 10 of the ’429 Patent in view of Braxton and Thompson

320. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

I. Pending Claim 296 of the ’171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

321. In my opinion, Pending Claim 296 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 296 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent

322. Pending Claim 296 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 296 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar

moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

323. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 296 is distinct from Claims 9 and 10 of the ’429 Patent.

324. A further distinction is that Pending Claim 296 also requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1 whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 296 of the '171 Application is patentably distinct from Claims 9 and 10 of the '429 Patent in view of Braxton and Thompson

325. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

J. Pending Claim 297 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

326. In my opinion, Pending Claim 297 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 297 of the '171 Application is different from Claims 9 and 10 of the '429 Patent

327. Pending Claim 297 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 297 further requires a hyaluronidase in the composition consists of amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

328. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 297 is distinct from Claims 9 and 10 of the '429 Patent.

2. Pending Claim 297 of the '171 Application is patentably distinct from Claims 9 and 10 of the '429 Patent in view of Braxton and Thompson

329. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D. In addition, mutation of an amino acid to a cysteine takes the sequence outside the scope of the referenced claim.

K. Pending Claim 298 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

330. In my opinion, Pending Claim 298 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 298 of the '171 Application is different from Claims 9 and 10 of the '429 Patent

331. Pending Claim 298 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 298 further requires a hyaluronidase glycoprotein that is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 or 36-482 of SEQ ID NO:1 in a mammalian cell.

332. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 298 is distinct from Claims 9 and 10 of the '429 Patent.

333. A further distinction is that Pending Claim 298 also requires a hyaluronidase glycoprotein that is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 of SEQ ID NO:1 in a mammalian cell whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 298 of the '171 Application is patentably distinct from Claims 9 and 10 of the '429 Patent in view of Braxton and Thompson

334. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D. In addition, mutation of an amino acid to a cysteine takes the sequence outside the scope of the referenced claim.

L. Pending Claim 300 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

335. In my opinion, Pending Claim 300 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 300 of the '171 Application is different from Claims 9 and 10 of the '429 Patent

336. Pending Claim 300 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 300 further requires a hyaluronidase polypeptide that has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4.

337. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 300 is distinct from Claims 9 and 10 of the '429 Patent.

338. A further distinction is that Pending Claim 300 also requires a hyaluronidase polypeptide that has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4 whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 300 of the '171 Application is patentably distinct from Claims 9 and 10 of the '429 Patent in view of Braxton and Thompson

339. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

M. Pending Claim 303 of the '171 Application is not an obvious variant of Claims 9 and 10 of U.S. Patent No. 7,767,429 in view of Braxton and Thompson

340. In my opinion, Pending Claim 303 of the '171 Application is different from Claims 9 and 10 of the '429 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 303 of the ’171 Application is different from Claims 9 and 10 of the ’429 Patent

341. Pending Claim 303 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 303 further requires a hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1.

342. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 303 is distinct from Claims 9 and 10 of the ’429 Patent.

343. A further distinction is that Pending Claim 303 also requires a hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1 whereas Claims 9 and 10 do not recite any such limitation.

2. Pending Claim 303 of the ’171 Application is patentably distinct from Claims 9 and 10 of the ’429 Patent in view of Braxton and Thompson

344. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

X. PENDING CLAIMS 264-266, 278, 291-293, 295-298, 300 AND 303 OF THE ’171 APPLICATION ARE NOT OBVIOUS VARIANTS OF CLAIMS 4 AND 5 OF U.S. PATENT NO. 7,846,431 IN VIEW OF BRAXTON AND THOMPSON

345. I understand that if the rejection of the Pending Claims under 35 U.S.C. § 103(a) is obviated, the rejections for obviousness-type double patenting over Claims 4 and 5 of U.S. Patent No. 7,846,431 (the “’431 Patent”) (A1944) in view of Braxton and Thompson must also

be obviated for the same reasons, since the Pending Claims cannot encompass obvious variants of the subject matter of the prior patents.

346. The Board agreed with the Examiner's obviousness-type double patenting rejection of Pending Claim 264 based on the finding that Claims 4 and 5 are directed to a hyaluronidase glycoprotein modified with a PEG polymer, and Braxton and Thompson teach three to six moieties. July 27, 2016 Decision on Appeal, at pp. 10-11 (A2220-A2221). The Examiner stated that "[b]ased on the teaching of both [Braxton and Thompson] …it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the PEGylation reaction for longest possible half-life and maximum activity." Examiner Reply, at p. 5 (A2178). The Examiner further incorporated the rejections under 35 U.S.C. § 103(a). *Id.* I disagree with this finding for the reasons set forth below.

347. In my opinion, secondary considerations of non-obviousness further evidence patentability of the Pending Claims of the '171 Application, including unexpected results, long-felt but unmet need, and industry praise and recognition, and each of these factors are commensurate in scope with the Pending Claims of the '171 Application as described further in Section XII below.

A. Pending Claim 264 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

348. In my opinion, Pending Claim 264 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 264 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

349. Below is a chart that compares Pending Claim 264 of the '171 Application with the earlier issued Claims 4 (or 5) of the '431 Patent:

Pending Claim 264, '171 Application	Claim 4, '431 Patent	Claim 5, '431 Patent
264. A pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein:	4. A pharmaceutical composition of claim 1, wherein the hyaluronidase glycoprotein is modified with a polymer.	5. A pharmaceutical composition of claim 4, wherein the polymer is PEG or dextran. 4. A pharmaceutical composition of claim 1, wherein the hyaluronidase glycoprotein is modified with a polymer.
the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule		
the hyaluronidase polypeptide is a human-derived hyaluronidase	1. A pharmaceutical composition, comprising: a) a hyaluronidase glycoprotein that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: (i) the hyaluronidase glycoprotein consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or (ii) the hyaluronidase glycoprotein contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-	1. A pharmaceutical composition, comprising: a) a hyaluronidase glycoprotein that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: (i) the hyaluronidase glycoprotein consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or (ii) the hyaluronidase glycoprotein contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence

	480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; and b) an insulin that comprises an insulin selected from among an insulin lispro, an insulin glargines, an NPH insulin and a recombinant insulin.	identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; and b) an insulin that comprises an insulin selected from among an insulin lispro, an insulin glargines, an NPH insulin and a recombinant insulin.
and the composition is formulated for systemic administration		

350. The plain text above illustrates the distinct nature of the claims.

351. A first distinction is that Pending Claim 264 requires a "hyaluronidase [that] contains about three to six PEG moieties per hyaluronidase molecule" whereas Claims 4 and 5 do not recite any such limitation.

352. A second distinction is that Pending Claim 264 requires that "the composition is formulated for systemic administration" whereas Claims 4 and 5 do not recite any such limitation.

353. In my opinion, one of ordinary skill would not understand that Claims 4 and 5 render obvious the claimed pharmaceutical composition formulated for systemic administration comprising a human-derived hyaluronidase that contains three to six PEG moieties per molecule. The claimed human-derived hyaluronidase contains many residues that could potentially be PEGylated, and as discussed above there are many additional variables that may lead to an uncertain outcome. For example, one of ordinary skill would not know whether 3-6 PEGs would retain sufficient activity and circulatory half-life to make it suitable for use as a pharmaceutical composition formulated for systemic administration as claimed in the '171 Application.

2. Pending Claim 264 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

354. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

B. Pending Claim 265 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

355. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 265 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

356. Pending Claim 265 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 265 further requires that the PEG moieties are branched.

357. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 265 is distinct from Claims 4 and 5 of the '431 Patent.

358. A further distinction is that Pending Claim 265 also requires that the PEG moieties are branched whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 265 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

359. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

C. Pending Claim 266 of the ’171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

360. In my opinion, Pending Claim 266 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 266 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent

361. Pending Claim 266 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 266 further requires that the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa), mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa).

362. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 266 is distinct from Claims 4 and 5 of the ’431 Patent.

363. A further distinction is that Pending Claim 266 also requires that the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa), mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS

(20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa) whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 266 of the ’171 Application is patentably distinct from Claims 4 and 5 of the ’431 Patent in view of Braxton and Thompson

364. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

D. Pending Claim 278 of the ’171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

365. In my opinion, Pending Claim 278 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 278 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent

366. The kit of Pending Claim 278 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. The kit of Pending Claim 278 further includes at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex.

367. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 278 is distinct from Claims 4 and 5 of the ’431 Patent.

368. A further distinction is that Pending Claim 278 also requires that the kit includes at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and optimally, instructions for delivering therapeutic substances or other

therapeutic molecule or macromolecular complex whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 278 of the ’171 Application is patentably distinct from Claims 4 and 5 of the ’431 Patent in view of Braxton and Thompson

369. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

E. Pending Claim 291 of the ’171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

370. In my opinion, Pending Claim 291 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 291 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent

371. Pending Claim 291 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 291 further requires that the PEG moiety results from reaction with mPEG-Succinimidyl Butanoate 30kD (mPEG-SBA (30kD)).

372. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 291 is distinct from Claims 4 and 5 of the ’431 Patent.

373. A further distinction is that Pending Claim 291 also requires that the PEG moiety results from reaction with mPEG-SBA (30kD) whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 291 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

374. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

F. Pending Claim 292 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

375. In my opinion, Pending Claim 292 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 292 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

376. Pending Claim 292 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 292 further requires that it is formulated for intravenous administration.

377. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 292 is distinct from Claims 4 and 5 of the '431 Patent.

378. A further distinction is that Pending Claim 292 also requires that that it is formulated for intravenous administration whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 292 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

379. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

G. Pending Claim 293 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

380. In my opinion, Pending Claim 293 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 293 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

381. Pending Claim 293 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 293 further requires that the PEGylated hyaluronidase is soluble and active at neutral pH.

382. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 293 is distinct from Claims 4 and 5 of the '431 Patent.

2. Pending Claim 293 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

383. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

H. Pending Claim 295 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

384. In my opinion, Pending Claim 295 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 295 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

385. Pending Claim 295 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 295 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar

moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1.

386. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 295 is distinct from Claims 4 and 5 of the ’431 Patent.

387. A further distinction is that Pending Claim 255 also requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1 whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 295 of the ’171 Application is patentably distinct from Claims 4 and 5 of the ’431 Patent in view of Braxton and Thompson

388. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

I. Pending Claim 296 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

389. In my opinion, Pending Claim 296 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 296 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

390. Pending Claim 296 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 296 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

391. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 296 is distinct from Claims 4 and 5 of the '431 Patent.

2. Pending Claim 296 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

392. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

J. Pending Claim 297 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

393. In my opinion, Pending Claim 297 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 297 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

394. Pending Claim 297 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 297 further requires a hyaluronidase in the composition consists of amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

395. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 297 is distinct from Claims 4 and 5 of the '431 Patent.

2. Pending Claim 297 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

396. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D. Moreover, such modifications of an existing amino acid to a cysteine would deviate from the amino acid sequence of the claimed human-derived hyaluronidase.

K. Pending Claim 298 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

397. In my opinion, Pending Claim 298 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 298 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent

398. Pending Claim 298 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 298 further requires a hyaluronidase glycoprotein that is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 or 36-482 of SEQ ID NO:1 in a mammalian cell.

399. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 298 is distinct from Claims 4 and 5 of the ’431 Patent.

400. A further distinction is that Pending Claim 298 also requires a hyaluronidase glycoprotein that is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 of SEQ ID NO:1 in a mammalian cell whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 298 of the ’171 Application is patentably distinct from Claims 4 and 5 of the ’431 Patent in view of Braxton and Thompson

401. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D. Moreover, such modifications of an existing amino acid to a cysteine would deviate from the amino acid sequence of the claimed human-derived hyaluronidase.

L. Pending Claim 300 of the ’171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

402. In my opinion, Pending Claim 300 of the ’171 Application is different from Claims 4 and 5 of the ’431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 300 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

403. Pending Claim 300 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 300 further requires a hyaluronidase polypeptide that has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4.

404. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 300 is distinct from Claims 4 and 5 of the '431 Patent.

405. A further distinction is that Pending Claim 300 also requires a hyaluronidase polypeptide that has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4 whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 300 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

406. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

M. Pending Claim 303 of the '171 Application is not an obvious variant of Claims 4 and 5 of U.S. Patent No. 7,846,431 in view of Braxton and Thompson

407. In my opinion, Pending Claim 303 of the '171 Application is different from Claims 4 and 5 of the '431 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 303 of the '171 Application is different from Claims 4 and 5 of the '431 Patent

408. Pending Claim 303 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 303 further requires a hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98%

amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1.

409. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 303 is distinct from Claims 4 and 5 of the '431 Patent.

410. A further distinction is that Pending Claim 303 also requires a hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1 whereas Claims 4 and 5 do not recite any such limitation.

2. Pending Claim 303 of the '171 Application is patentably distinct from Claims 4 and 5 of the '431 Patent in view of Braxton and Thompson

411. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

XI. PENDING CLAIMS 264-266, 278, 291-293, 295-298, 300 AND 303 OF THE '171 APPLICATION ARE NOT OBVIOUS VARIANTS OF CLAIMS 5 AND 6 OF U.S. PATENT NO. 7,829,081 IN VIEW OF BRAXTON AND THOMPSON

412. I understand that if the rejection of the Pending Claims under 35 U.S.C. § 103(a) is obviated, the rejections for obviousness-type double patenting over Claims 5 and 6 of U.S. Patent No. 7,829,081 (the "'081 patent") (A2170) in view of Braxton and Thompson must also be obviated for the same reasons, since the Pending Claims cannot encompass obvious variants of the subject matter of the prior patents.

413. The Board agreed with the Examiner's obviousness-type double patenting rejection of Pending Claim 264 based on the finding that Claims 5 and 6 are directed to a composition comprising a hyaluronidase glycoprotein modified with a PEG polymer, and Braxton and Thompson teach three to six moieties. July 27, 2016 Decision on Appeal, at p. 11

(A2221). The Examiner stated that "[b]ased on the teaching of both [Braxton and Thompson] …it would have been obvious to one of ordinary skill in the art at the time of invention to optimize the PEGylation reaction for longest possible half-life and maximum activity." Examiner Reply, at p. 6 (A2179). The Examiner further incorporated the rejections under 35 U.S.C. § 103(a). *Id.* I disagree with this finding for the reasons set forth below.

414. In my opinion, secondary considerations of non-obviousness further evidence patentability of the Pending Claims of the '171 Application, including unexpected results, long-felt but unmet need, and industry praise and recognition, and each of these factors are commensurate in scope with the Pending Claims of the '171 Application as described further in Section XII below.

A. Pending Claim 264 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

415. In my opinion, Pending Claim 264 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 264 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

416. Below is a chart that compares Pending Claim 264 of the '171 Application with the earlier issued Claims 5 (or 5) of the '081 Patent:

Pending Claim 264, '171 Application	Claim 4, '431 Patent	Claim 5, '431 Patent
264. A pharmaceutical composition, comprising a PEGylated hyaluronidase in a pharmaceutically acceptable carrier, wherein:	5. A pharmaceutical composition of claim 1, wherein the hyaluronidase glycoprotein is modified with a polymer.	6. A pharmaceutical composition of claim 5, wherein the polymer is PEG or dextran.. 5. A pharmaceutical composition of claim 1, wherein the hyaluronidase glycoprotein is modified

		with a polymer.
the hyaluronidase contains about three to six PEG moieties per hyaluronidase molecule		
the hyaluronidase polypeptide is a human-derived hyaluronidase	1. A pharmaceutical composition, comprising: a) a hyaluronidase glycoprotein that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: (i) the hyaluronidase glycoprotein consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or (ii) the hyaluronidase glycoprotein contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; and b) a cosmetic agent.	1. A pharmaceutical composition, comprising: a) a hyaluronidase glycoprotein that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: (i) the hyaluronidase glycoprotein consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or (ii) the hyaluronidase glycoprotein contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; and b) a cosmetic agent.
and the composition is formulated for systemic administration		

417. The plain text above illustrates the distinct nature of the claims.

418. A first distinction is that Pending Claim 264 requires a "hyaluronidase [that] contains about three to six PEG moieties per hyaluronidase molecule" whereas Claims 5 and 6 do not recite any such limitation.

419. A second distinction is that Pending Claim 264 requires that "the composition is formulated for systemic administration" whereas Claims 5 and 6 do not recite any such limitation.

420. In my opinion, one of ordinary skill would not understand that Claims 5 and 6 render obvious the claimed pharmaceutical composition formulated for systemic administration comprising a human-derived hyaluronidase that contains three to six PEG moieties per molecule. The claimed human-derived hyaluronidase contains many residues that could potentially be PEGylated, and as discussed above there are many additional variables that may lead to an uncertain outcome. For example, one of ordinary skill would not know whether 3-6 PEGs would retain sufficient activity and circulatory half-life to make it suitable for use as a pharmaceutical composition formulated for systemic administration as claimed in the '171 Application.

2. Pending Claim 264 of the '171 Application is patentably distinct from Claims 5 and 6 of the '081 Patent in view of Braxton and Thompson

421. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

B. Pending Claim 265 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

422. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

423. Pending Claim 265 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 265 further requires that the PEG moieties are branched.

424. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 265 is distinct from Claims 5 and 6 of the '081 Patent.

425. A further distinction is that Pending Claim 265 also requires that the PEG moieties are branched whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 265 of the '171 Application is patentably distinct from Claims 5 and 6 of the '081 Patent in view of Braxton and Thompson

426. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

C. Pending Claim 266 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

427. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 266 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

428. Pending Claim 266 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 266 further requires that the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa),

mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa).

429. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 266 is distinct from Claims 5 and 6 of the ’081 Patent.

430. A further distinction is that Pending Claim 266 also requires that the PEG moieties result from reaction with a PEG reagent selected from among mPEG-succinimidyl butanoate (mPEG-SBA) (5kDa), mPEG-SBA (20kDa), mPEG-SBA (30kDa), mPEG-succinimidyl α-methylbutanoate (mPEG-SMB) (20kDa), mPEG-SMB (30kDa), mPEG-butyraldehyde (30kDa), mPEG-succinimidyl propionate (mPEG-SPA) (20kDa), mPEG-SPA (30kDa), mPEG2-N-Hydroxylsuccinimide (mPEG2-NHS) (10kDa branched), mPEG2-NHS (20kDa branched), mPEG2-NHS (40kDa branched), mPEG2-NHS (60kDa branched), PEG-NHS-biotin (5kDa biotinylated), PEG-p-nitrophenyl-carbonate (30kDa) and PEG-proprionaldehyde (30kDa) whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 266 of the ’171 Application is patentably distinct from Claims 5 and 6 of the ’081 Patent in view of Braxton and Thompson

431. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

D. Pending Claim 278 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

432. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 278 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

433. The kit of Pending Claim 278 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. The kit of Pending Claim 278 further includes at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex.

434. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 278 is distinct from Claims 5 and 6 of the '081 Patent.

435. A further distinction is that Pending Claim 278 also requires that the kit includes at least one therapeutic substance or other therapeutic molecule or macromolecular complex in an acceptable carrier; and optimally, instructions for delivering therapeutic substances or other therapeutic molecule or macromolecular complex whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 278 of the '171 Application is patentably distinct from Claims 5 and 6 of the '081 Patent in view of Braxton and Thompson

436. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

E. Pending Claim 291 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

437. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 291 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

438. Pending Claim 291 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 291 further requires that the PEG moiety results from reaction with mPEG-Succinimidyl Butanoate 30kD (mPEG-SBA (30kD)).

439. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 291 is distinct from Claims 5 and 6 of the '081 Patent.

440. A further distinction is that Pending Claim 291 also requires that the PEG moiety results from reaction with mPEG-SBA (30kD) whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 291 of the '171 Application is patentably distinct from Claims 5 and 6 of the '081 Patent in view of Braxton and Thompson

441. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

F. Pending Claim 292 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

442. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 292 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent

443. Pending Claim 292 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 292 further requires that it is formulated for intravenous administration.

444. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 292 is distinct from Claims 5 and 6 of the ’081 Patent.

445. A further distinction is that Pending Claim 292 also requires that it is formulated for intravenous administration whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 292 of the ’171 Application is patentably distinct from Claims 5 and 6 of the ’081 Patent in view of Braxton and Thompson

446. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

G. Pending Claim 293 of the ’171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

447. In my opinion, Pending Claim 265 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 293 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent

448. Pending Claim 293 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 293 further requires that the PEGylated hyaluronidase is soluble and active at neutral pH.

449. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 293 is distinct from Claims 5 and 6 of the ’081 Patent.

2. Pending Claim 293 of the '171 Application is patentably distinct from Claims 5 and 6 of the '081 Patent in view of Braxton and Thompson

450. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

H. Pending Claim 295 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

451. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 295 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

452. Pending Claim 295 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 295 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1.

453. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 295 is distinct from Claims 5 and 6 of the '081 Patent.

454. A further distinction is that Pending Claim 295 also requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently

attached to an asparagine (N) residue of the hyaluronidase polypeptide, wherein: the hyaluronidase polypeptide is a C-terminal truncated polypeptide of SEQ ID NO:1; and contains amino acid residues 36-464 as set forth in SEQ ID NO:1 but does not include the complete sequence of amino acids set forth in SEQ ID NO:1 or contains a sequence of amino acid residues that has at least 95% amino acid sequence identity with the sequence of amino acids 36-464 set forth in SEQ ID NO:1 whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 295 of the ’171 Application is patentably distinct from Claims 5 and 6 of the ’081 Patent in view of Braxton and Thompson

455. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

I. Pending Claim 296 of the ’171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

456. In my opinion, Pending Claim 265 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 296 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent

457. Pending Claim 296 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 296 further requires a PEGylated hyaluronidase that is active at neutral pH and contains at least one sugar moiety that is covalently attached to an asparagine (N) residue of the hyaluronidase polypeptide; and a) the hyaluronidase consists of the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1; or b) the hyaluronidase contains amino acid substitutions in the sequence of amino acids set forth as amino acids 36-477,

36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1, whereby the amino acid-substituted hyaluronidase glycoprotein consists of a sequence of amino acids that has at least 95% amino acid sequence identity with the sequence of amino acids set forth as amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

458. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 296 is distinct from Claims 5 and 6 of the ’081 Patent.

2. Pending Claim 296 of the ’171 Application is patentably distinct from Claims 5 and 6 of the ’081 Patent in view of Braxton and Thompson

459. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

J. Pending Claim 297 of the ’171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

460. In my opinion, Pending Claim 265 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 297 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent

461. Pending Claim 297 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 297 further requires a hyaluronidase in the composition consists of amino acids 36-477, 36-478, 36-479, 36-480, 36-481, 36-482, or 36-483 of SEQ ID NO:1.

462. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 297 is distinct from Claims 5 and 6 of the ’081 Patent.

2. Pending Claim 297 of the ’171 Application is patentably distinct from Claims 5 and 6 of the ’081 Patent in view of Braxton and Thompson

463. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D. Moreover, such modifications of an existing amino acid to a cysteine would deviate from the amino acid sequence of the claimed human-derived hyaluronidase.

K. Pending Claim 298 of the ’171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

464. In my opinion, Pending Claim 265 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 298 of the ’171 Application is different from Claims 5 and 6 of the ’081 Patent

465. Pending Claim 298 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 298 further requires a hyaluronidase glycoprotein that is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 or 36-482 of SEQ ID NO:1 in a mammalian cell.

466. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 298 is distinct from Claims 5 and 6 of the ’081 Patent.

467. A further distinction is that Pending Claim 298 also requires a hyaluronidase glycoprotein that is produced by expression of a nucleic acid molecule that encodes amino acids 1-482 of SEQ ID NO:1 in a mammalian cell whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 298 of the '171 Application is patentably distinct from Claims 5 and 6 of the '081 Patent in view of Braxton and Thompson

468. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D. Moreover, such modifications of an existing amino acid to a cysteine would deviate from the amino acid sequence of the claimed human-derived hyaluronidase.

L. Pending Claim 300 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

469. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 300 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

470. Pending Claim 300 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 300 further requires a hyaluronidase polypeptide that has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4.

471. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 300 is distinct from Claims 5 and 6 of the '081 Patent.

472. A further distinction is that Pending Claim 300 also requires a hyaluronidase polypeptide that has a sequence of amino acids that has [at] least 95% sequence identity to the sequence set forth in SEQ ID NO:4 whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 300 of the '171 Application is patentably distinct from Claims 5 and 6 of the '081 Patent in view of Braxton and Thompson

473. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

M. Pending Claim 303 of the '171 Application is not an obvious variant of Claims 5 and 6 of U.S. Patent No. 7,829,081 in view of Braxton and Thompson

474. In my opinion, Pending Claim 265 of the '171 Application is different from Claims 5 and 6 of the '081 Patent, and these differences render the claims patentably distinct.

1. Pending Claim 303 of the '171 Application is different from Claims 5 and 6 of the '081 Patent

475. Pending Claim 303 depends on Pending Claim 264 and thus, includes every limitation of the pharmaceutical composition of Pending Claim 264. Pending Claim 303 further requires a hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1.

476. For at least the reasons discussed above with respect to Pending Claim 264, Pending Claim 303 is distinct from Claims 5 and 6 of the '081 Patent.

477. A further distinction is that Pending Claim 303 also requires a hyaluronidase polypeptide consists of a sequence of amino acids that has at least 98% amino acid sequence identity with the sequence of amino acids set forth as residues 36-483 in SEQ ID NO:1 whereas Claims 5 and 6 do not recite any such limitation.

2. Pending Claim 303 of the ’171 Application is patentably distinct from Claims 5 and 6 of the ’081 Patent in view of Braxton and Thompson

478. One of ordinary skill would not have used the teachings of Braxton and Thompson to make the claimed PEGylated human-derived hyaluronidase with three to six PEG moieties for the same reasons discussed previously in Section VIII.A-D.

XII. SECONDARY FACTORS OF NONOBVIOUSNESS

479. There are additional factors that further support my opinion that the asserted claims remain valid over all the references identified by the Examiner, and later affirmed by the PTO. I understand that these objective factors are sometimes referred to as secondary considerations of nonobviousness, and that these secondary considerations may often establish that an invention appearing to have been obvious in light of the prior art, was not.

480. I understand that these secondary considerations include long-felt but unmet need, the failure of others, skepticism by experts, praise by others, teaching away by others, unexpected results of the invention, recognition of a problem, copying of the invention by competitors, and the invention’s commercial success. I understand that each of these considerations may form an independent basis for nonobviousness of a patent.

481. I considered secondary considerations of nonobviousness for the ‘’171 Application, and in my opinion, and for the reasons below, these secondary considerations further support the conclusion that each of the Pending Claims of the ’171 Application is non-obvious. Additionally, in my opinion, there is a direct nexus between each secondary consideration discussed below and the Pending Claims. The evidence that establishes the validity of the ’171 Application could be discussed under various categories of secondary considerations of nonobviousness. Just because I may expressly discuss below certain evidence

under a particular category of secondary considerations of nonobviousness does not exclude that such evidence from supporting another category.

A. Unexpected Results

482. I understand that one secondary factor considered with regard to nonobviousness is unexpected results achieved by the invention.

483. As I explained above, the molecular weight of each individual PEG moiety and the total molecular weight of the end product conjugate have a great impact on the activity of enzymes with large macromolecular substrates. For such enzymes, smaller molecular weight PEGs are generally preferred to preserve enzyme activity. Additionally, mono-PEGylation is particularly preferred via site-specific modification to minimize activity impairment.

484. rHuPH20 is already a large enzyme in its native form that catalyzes a macromolecular substrate, hyaluronan. Based on the general principles explained above, one of ordinary skill would expect that in such case, smaller molecular weight PEG moieties and fewer PEGs, with a preference to mono-PEGylation would be required to balance the need to increase half-life while retaining sufficient enzymatic activity for use as a therapeutic.

485. In my opinion, the inventors' data showing that the attachment of up to 3-5 PEG moieties, each of molecular weight 30 kDa, was required to achieve maximum increase in half-life while still retaining substantial enzymatic activity is a surprising and unexpected result. Bookbinder Declaration, at pp. 6-7, (A1621-A1628, at A1626-A1627); *see also* '171 Application, Example 21-A (A229-A233). To me, this is an unusually high number to retain such enzymatic activity considering the large molecular weight of the enzyme and substrate.

486. The claimed PEGylated rHuPH20 of the '171 Application overcomes problems associated with systemic administration of native rHuPH20 as claimed in '140 Bookbinder,

namely short half-life and insufficient enzymatic activity. Importantly, it is the addition of 3-6 PEG moieties that retains the necessary properties (i.e., increase half-life while retaining sufficient enzymatic activity) to make it useful as a therapeutic or pharmaceutical composition for systemic administration as claimed in the '171 Application.

487. None of the cited references, singly or in combination, teach or suggest that 3-6 PEG moieties as claimed in the PEGylated rHuPH20 of the '171 Application is important and necessary to achieve the balance of significantly increasing half-life while retaining sufficient enzymatic activity for use as a therapeutic.

B. Long Felt Need

488. I understand that another such secondary consideration is long-felt but unmet need. In such a consideration, the nature of the problem that persisted in the art, and the inventor(s)' solution, are factors to be considered in determining whether the invention would have been obvious to a person having ordinary skill in the art. I have read the Flamion Report addressing the long-felt need and rely on and incorporate that analysis as further support for my opinions.

C. Industry Praise and Recognition

489. I also understand that praise of the invention by those skilled in the relevant industry indicates that the invention is not obvious. I have read the Flamion Report addressing Industry Praise and Recognition and rely on and incorporate that analysis as further support for my opinions.

D. The Secondary Factors are Commensurate in Scope with the Pending Claims of the '171 Application

490. The Pending Claims of the '171 Application recite a pharmaceutical composition formulated for systemic administration comprising a PEGylated rHuPH20 with about three to six PEG moieties per hyaluronidase molecule.

491. Thus, the claimed PEGylated rHuPH20 with three to six PEG moieties (PEGPH20) achieves a half-life that is long enough (that the native rHuPH20 is unable to achieve on its own) such that when it is administered systemically, such as intravenously, it is able to reach its target, such as a tumor, without destroying its enzymatic activity and ability to deplete hyaluronan to increase intratumoral perfusion and drug delivery for use as a therapeutic.

492. Each of the secondary factors recited above are directly linked to the ability of PEGPH20 to deplete hyaluronan in a tumor microenvironment as a result of the 3-6 PEG moieties attached to rHuPH20 making it suitable for use as a pharmaceutical composition for systemic administration.

493. Accordingly, in my opinion, there is a nexus between the claimed invention of the '171 Application and the secondary considerations of non-obviousness described above.

Executed this 15 day of May, 2017

Samuel Zalipsky

Samuel Zalipsky, Ph.D.

DM_US 83202141-1.086262.0015

CORRECTED
EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

HALOZYME, INC. Plaintiff v. JOSEPH MATAL, performing the functions and duties of Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, Defendant.	Civil Action No. 16-CV-01580 (CMH/JFA)

CORRECTED LIST OF MATERIALS CONSIDERED FOR OPENING EXPERT REPORT OF SAMUEL ZALIPSKY, Ph.D., REGARDING NON-OBVIOUSNESS OF THE PENDING CLAIMS OF THE '171 APPLICATION

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No.	Date of Document	Document Description	Bates Range / Exhibit No.
1.	7/22/2013	Pending Claims of the '171 Application (Appeal Brief)	Corrected Exhibit 1 A1248-A1250
2.	Spring 2017	Samuel Zalipsky, Ph.D. CV	Exhibit 2
3.		Zalispsky List of Materials Considered	Exhibit 3
4.	7/27/2016	PTAB Decision of Appeal	Exhibit 4 A2210-A2222
5.	09/16/2004	WO 2004/078140 Bookbinder et al. ("'140 Bookbinder")	Exhibit 5 A1332-A1546
6.	6/16/1998	U.S. Patent No. 5,766,897 ("Braxton")	Exhibit 6 A1547-A1581
7.	4/22/2003	U.S. Patent No. 6,552,170 ("Thompson")	Exhibit 7 A1596-A1620
8.	5/15/2017	Initial Expert Report of Bruno Flamion, M.D., Ph.D.	N/A
9.	12/19/2016	Complaint	Dkt. No. 1
10.	2/21/2017	Answer	Dkt. No. 17
11.	9/27/2005 – 1/17/2017	File History '171 Patent Application	A1 – A2243
12.	12/20/2012 – 10/20/2016	Appeal Briefings – Appeal No. 2014-001770	A1191-A2239
13.	9/27/2016	Request for Rehearing	A2223-A2235
14.	10/20/2016	Decision on Request for Rehearing	A2236-A2239
15.	09/27/2005	U.S. Patent Application Serial No. 11/238,171	A1-A324
16.	8/3/2010	U.S. Patent No. 7,767,429	A1629-A1720
17.	12/7/2010	U.S. Patent No. 7,846,431	A1831-A1946
18.	11/9/2010	U.S. Patent No. 7,829,081	A2057-A2170
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